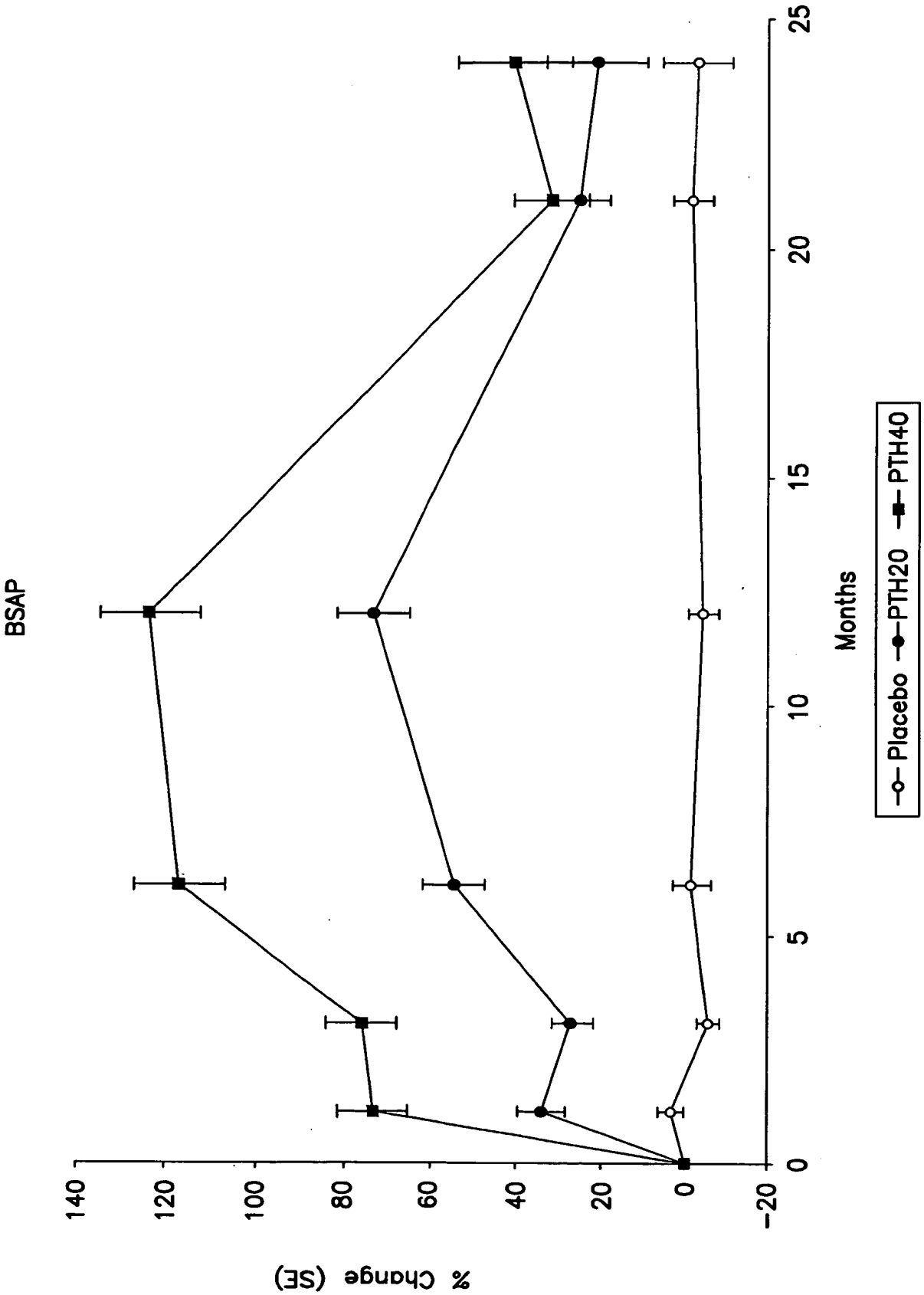

BSAP
% Change (SE)
140
120
100
80
60
40
20
0
-20
0
5
10
15
20
25
Months
Placebo
PTH20
PTH40

FIG. 1

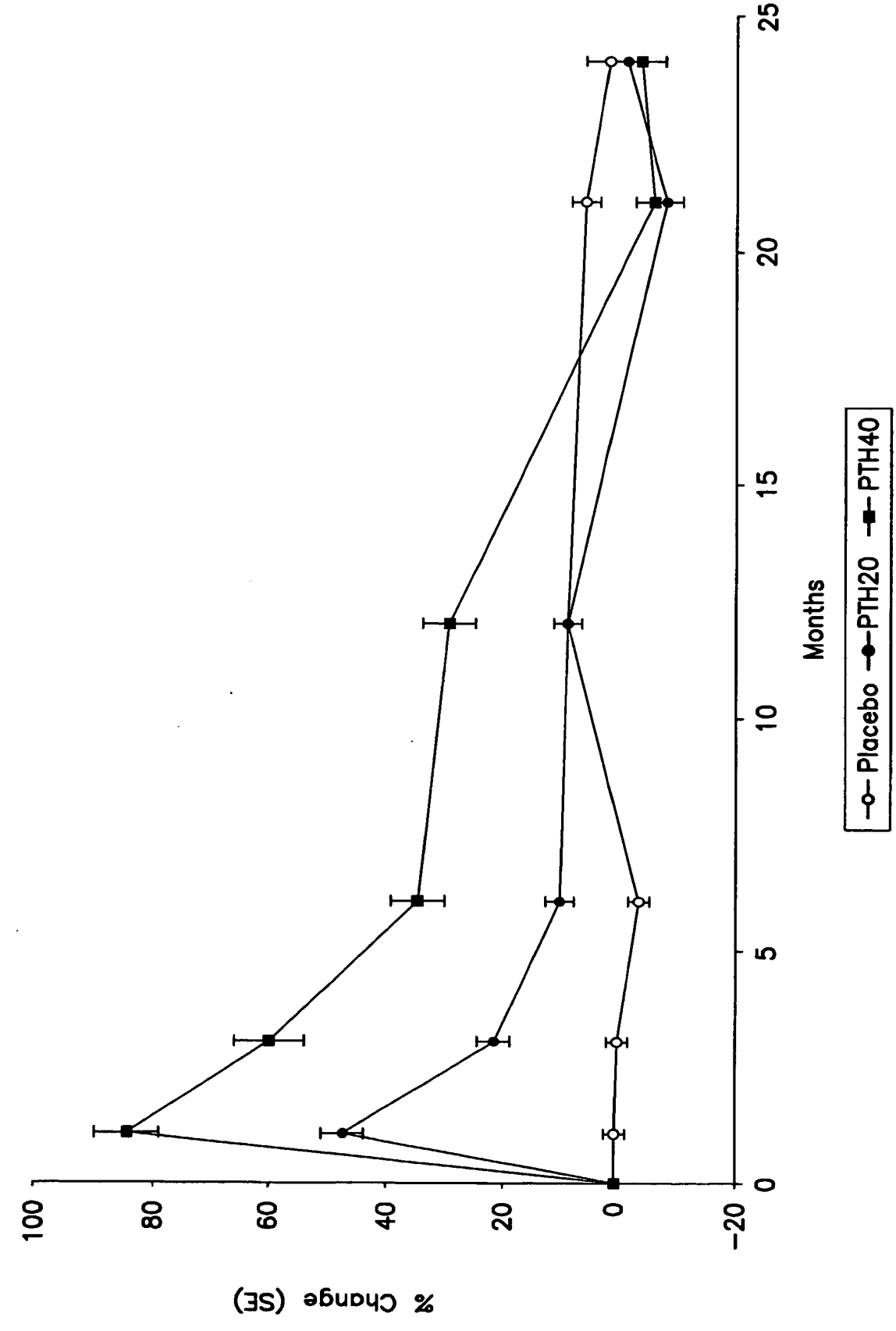

PICP
% Change (SE)
100
80
60
40
20
0
-20
0
5
10
15
20
25
Months
Placebo
PTH20
PTH40

FIG. 2

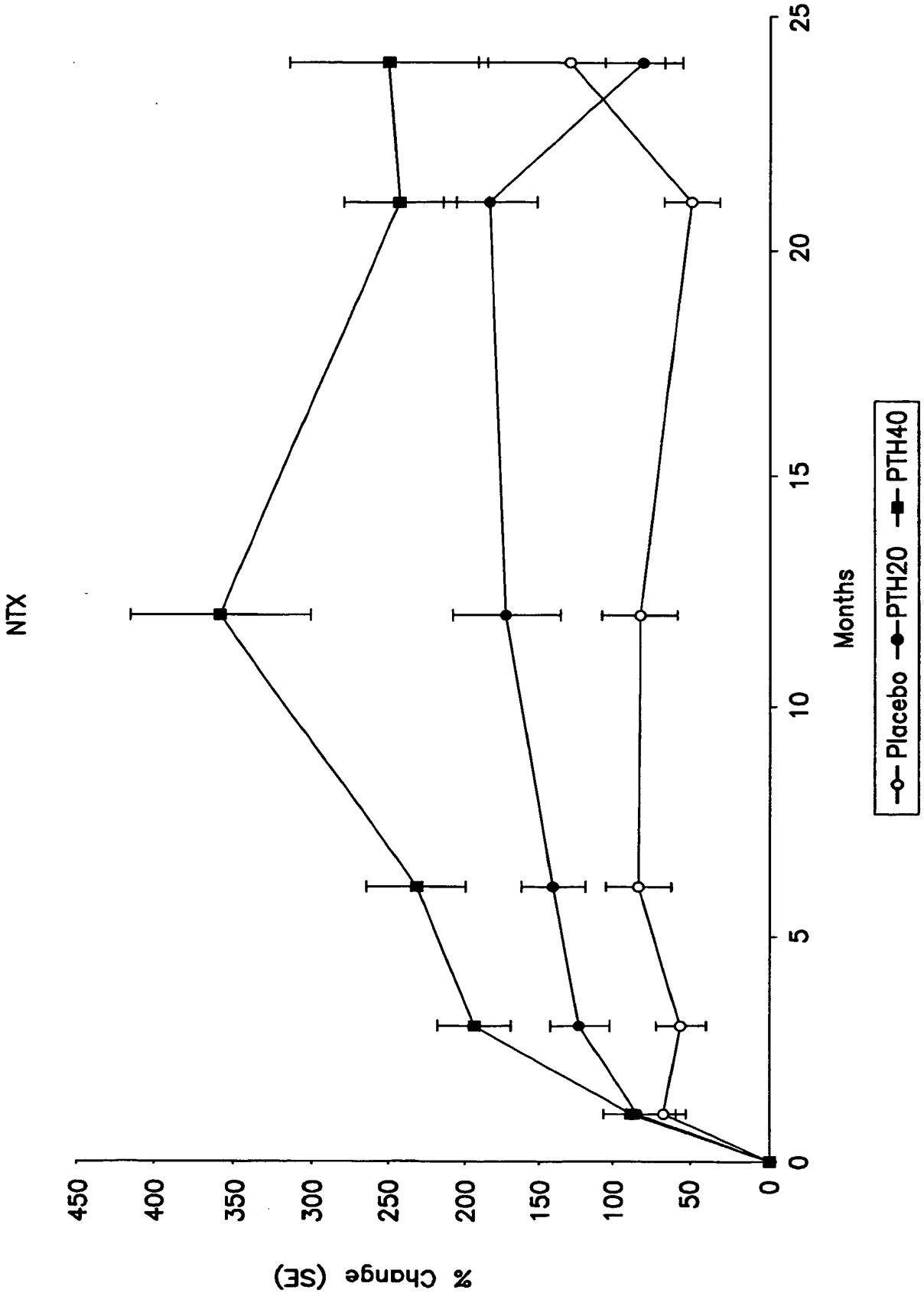

NTX
% Change (SE)
450
400
350
300
250
200
150
100
50
0
0
5
10
15
20
25
Months
Placebo
PTH20
PTH40

FIG. 3

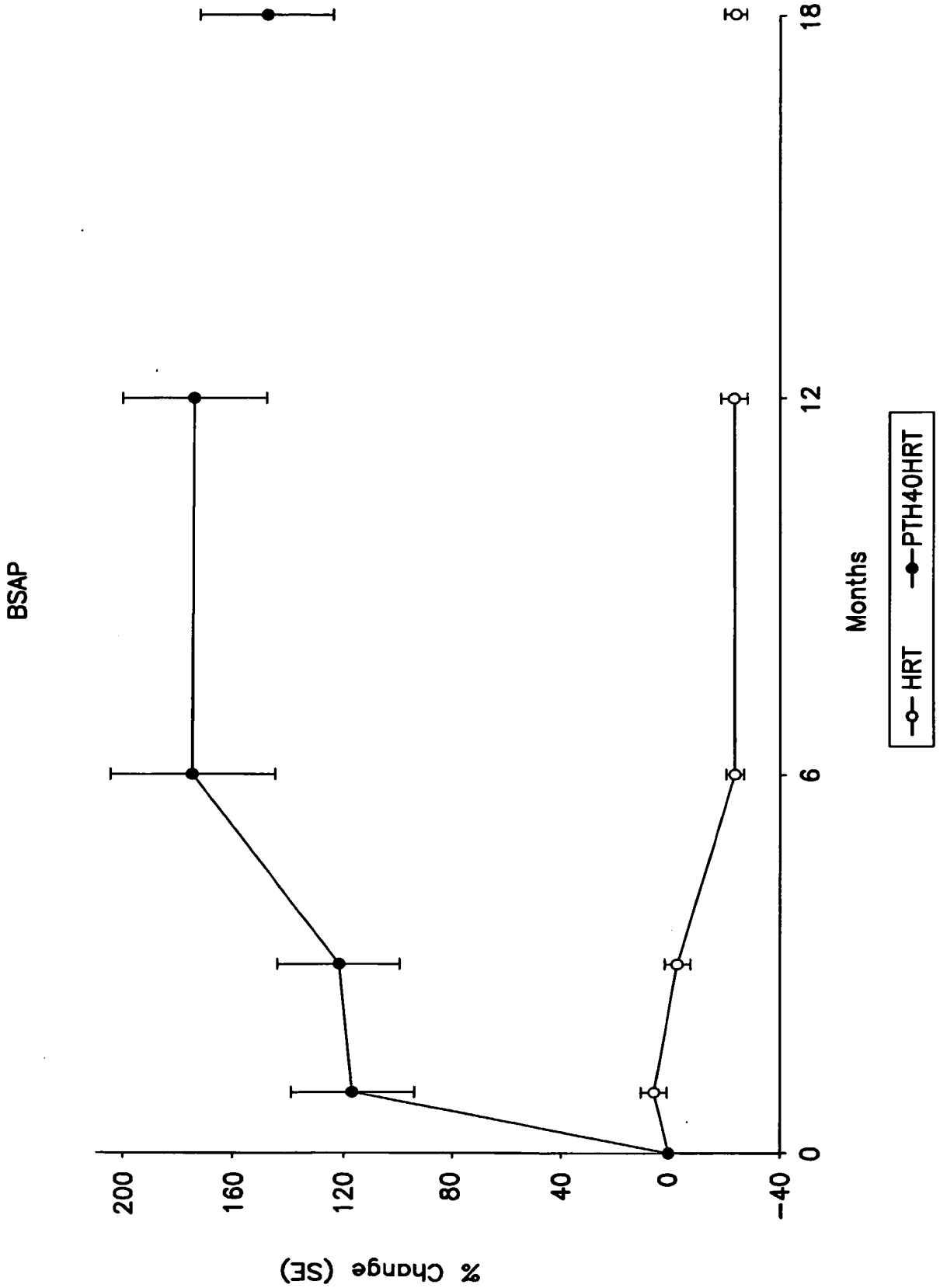

BSAP
% Change (SE)
200
160
120
80
40
0
-40
0
6
12
18
Months
HRT
PTH40HRT

FIG. 4

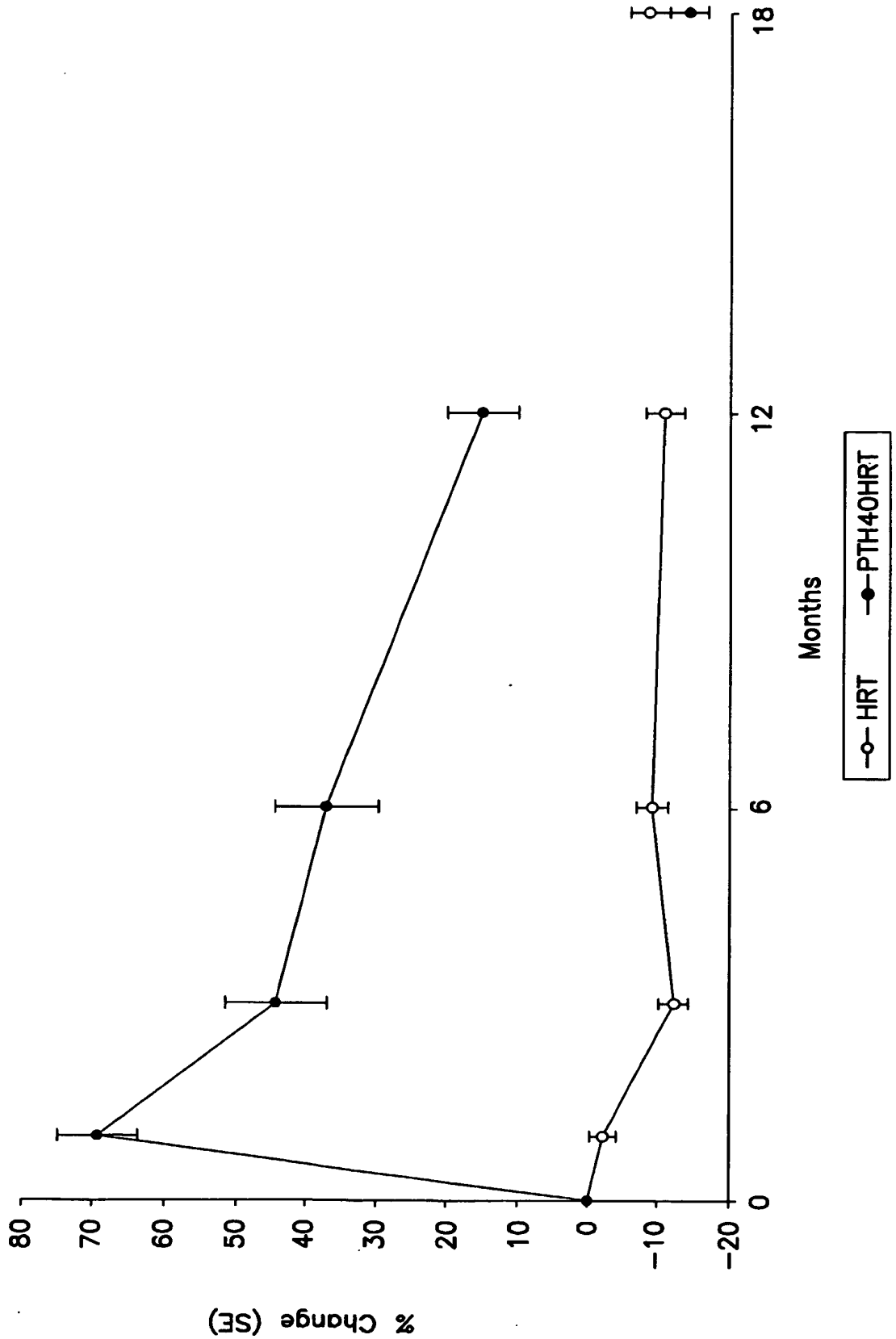

PICP
% Change (SE)
80
70
60
50
40
30
20
10
0
−10
−20
0
6
12
18
Months
HRT
PTH40HRT

FIG. 5

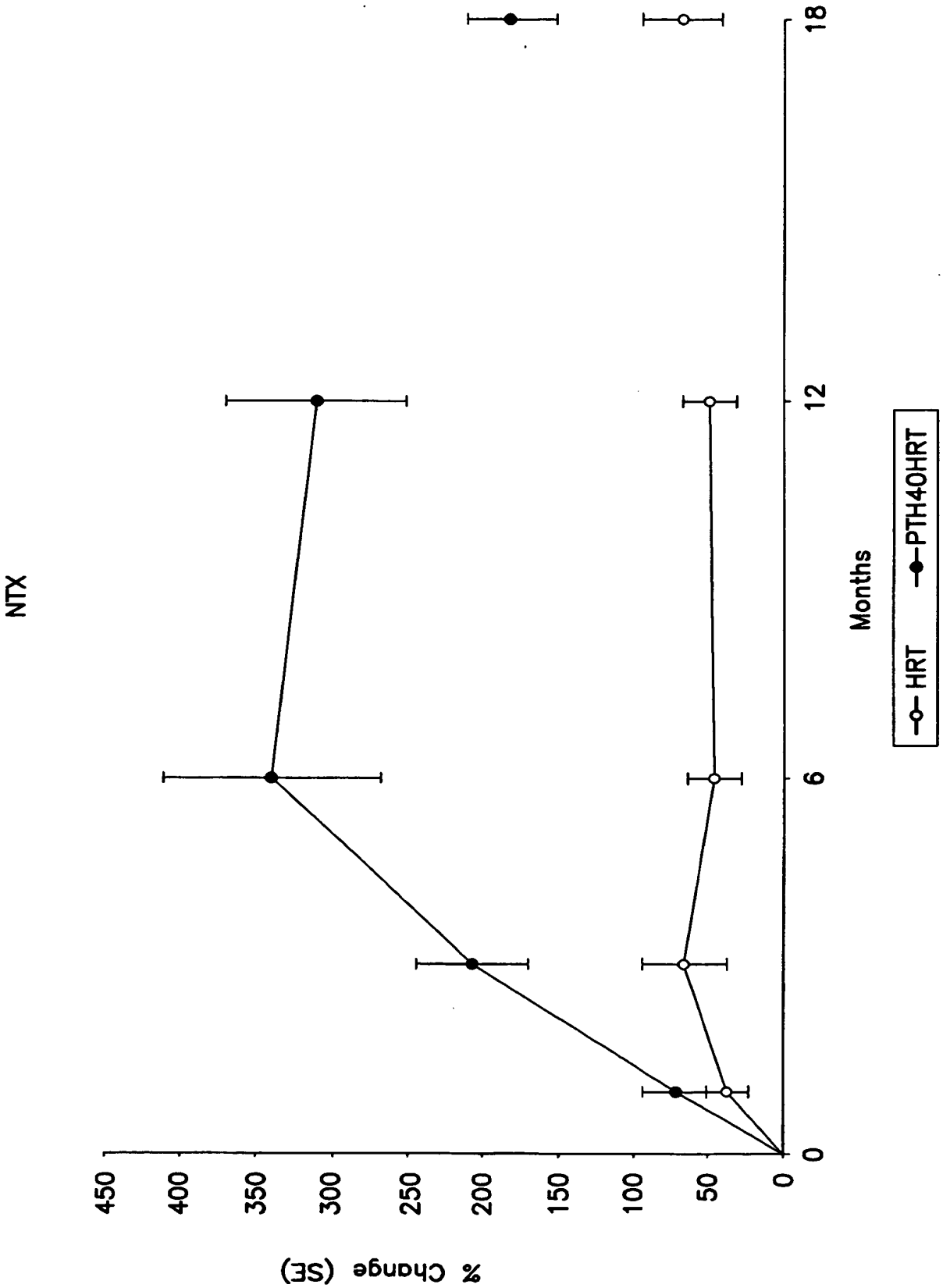

NTX
% Change (SE)
450
400
350
300
250
200
150
100
50
0
0
6
12
18
Months
HRT
PTH40HRT

FIG. 6

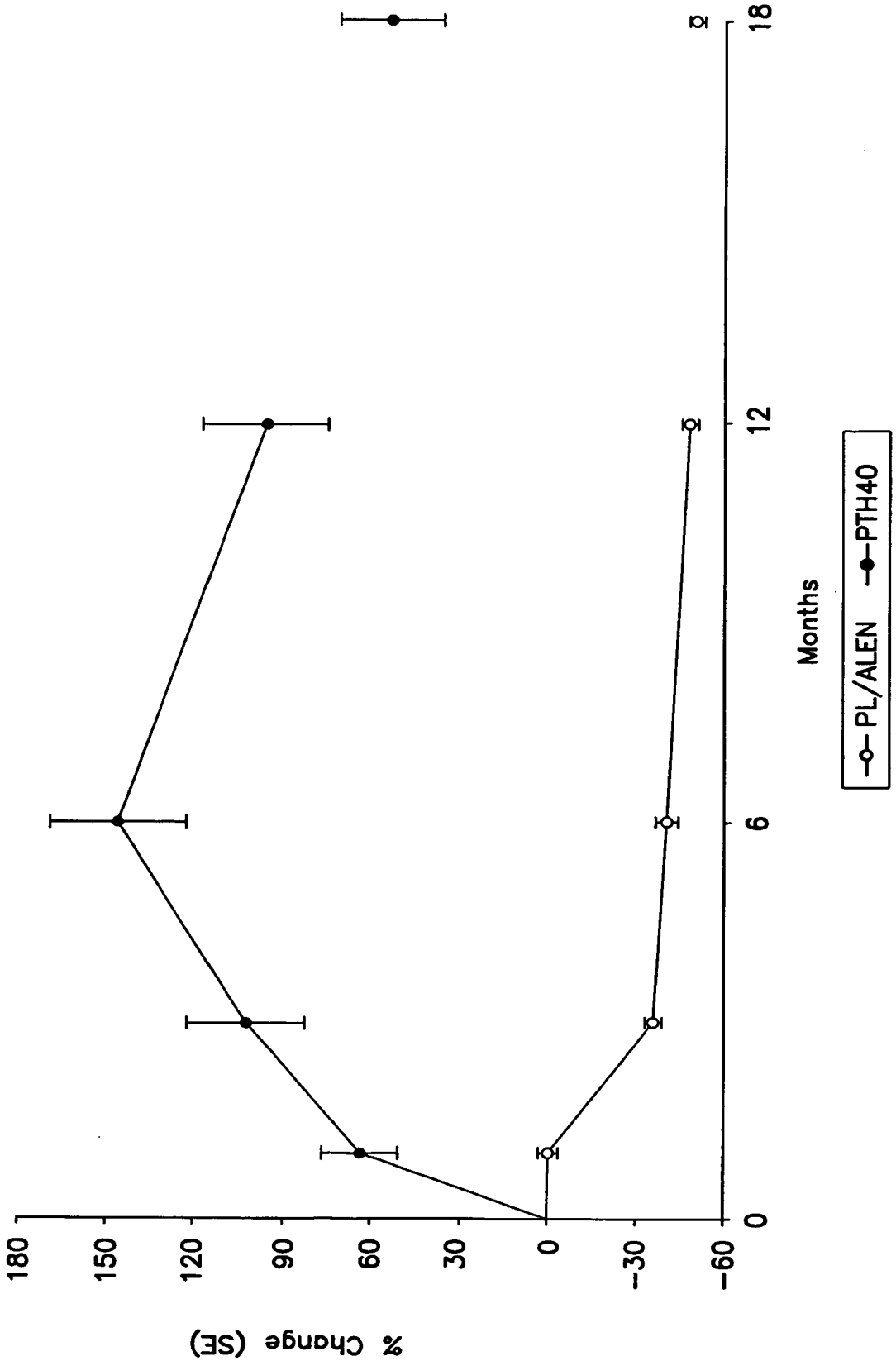

BSAP
% Change (SE)
180
150
120
90
60
30
0
-30
-60
0
6
12
18
Months
PL/ALEN
PTH40

FIG. 7

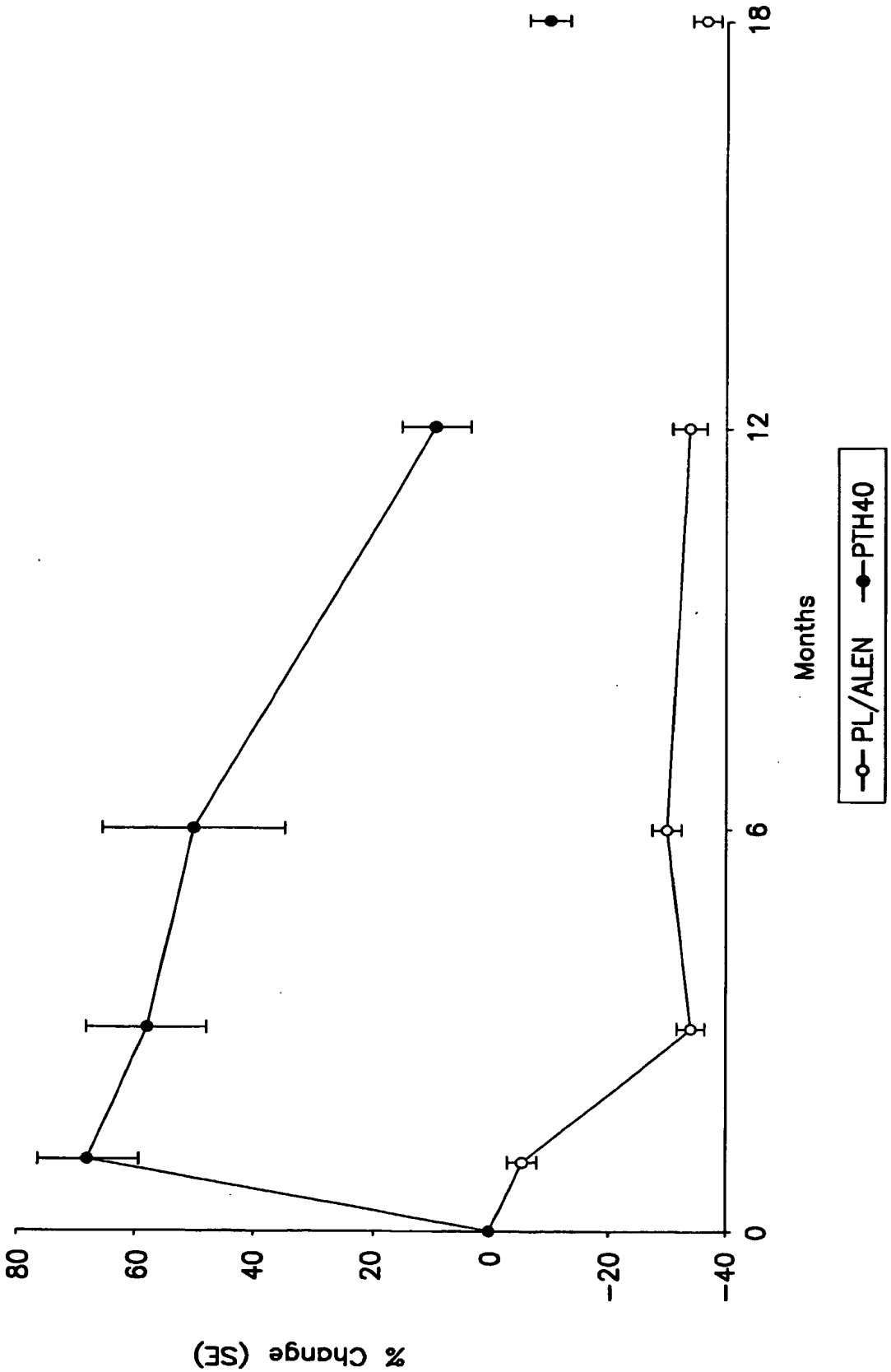


FIG. 8

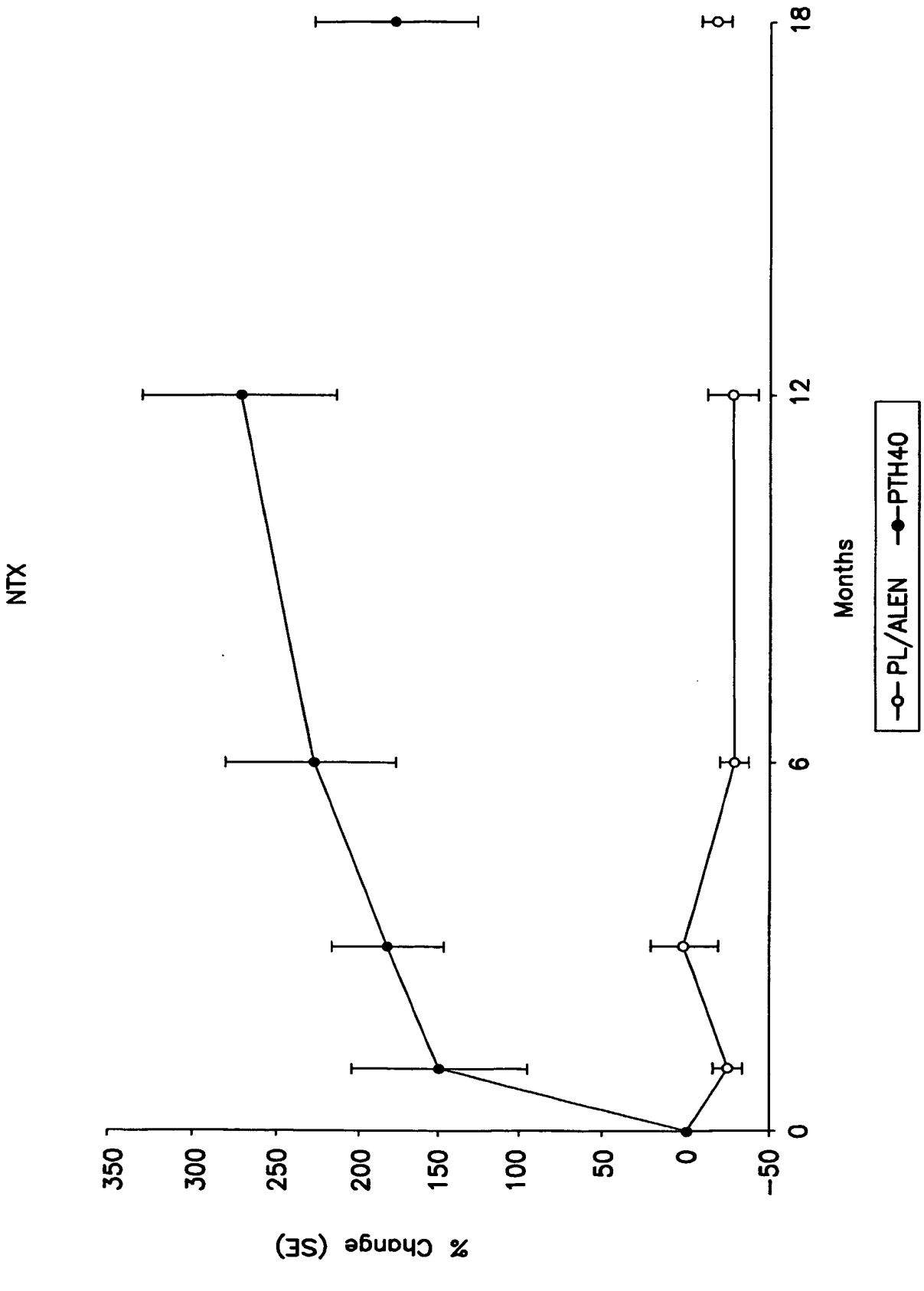

NTX
% Change (SE)
350
300
250
200
150
100
50
0
-50
0
6
12
18
Months
PL/ALEN
PTH40

FIG. 9

FIG. 10

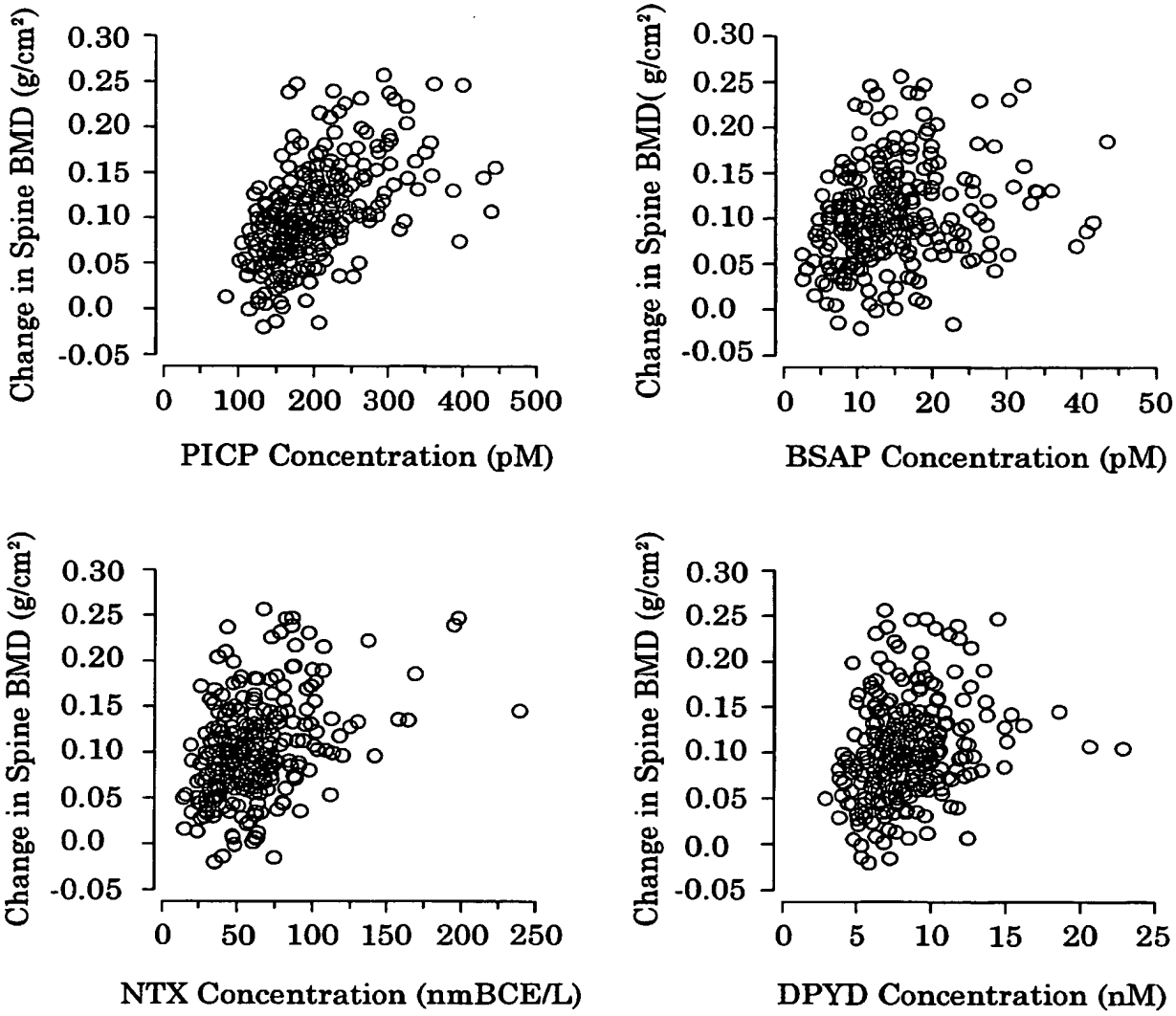

Change in Spine BMD (g/cm²)
0.30
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
0 100 200 300 400 500
PICP Concentration (pM)
Change in Spine BMD(g/cm²)
0.30
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
0 10 20 30 40 50
BSAP Concentration (pM)
Change in Spine BMD (g/cm²)
0.30
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
0 50 100 150 200 250
NTX Concentration (nmBCE/L)
Change in Spine BMD (g/cm²)
0.30
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
0 5 10 15 20 25
DPYD Concentration (nM)

FIG. 11

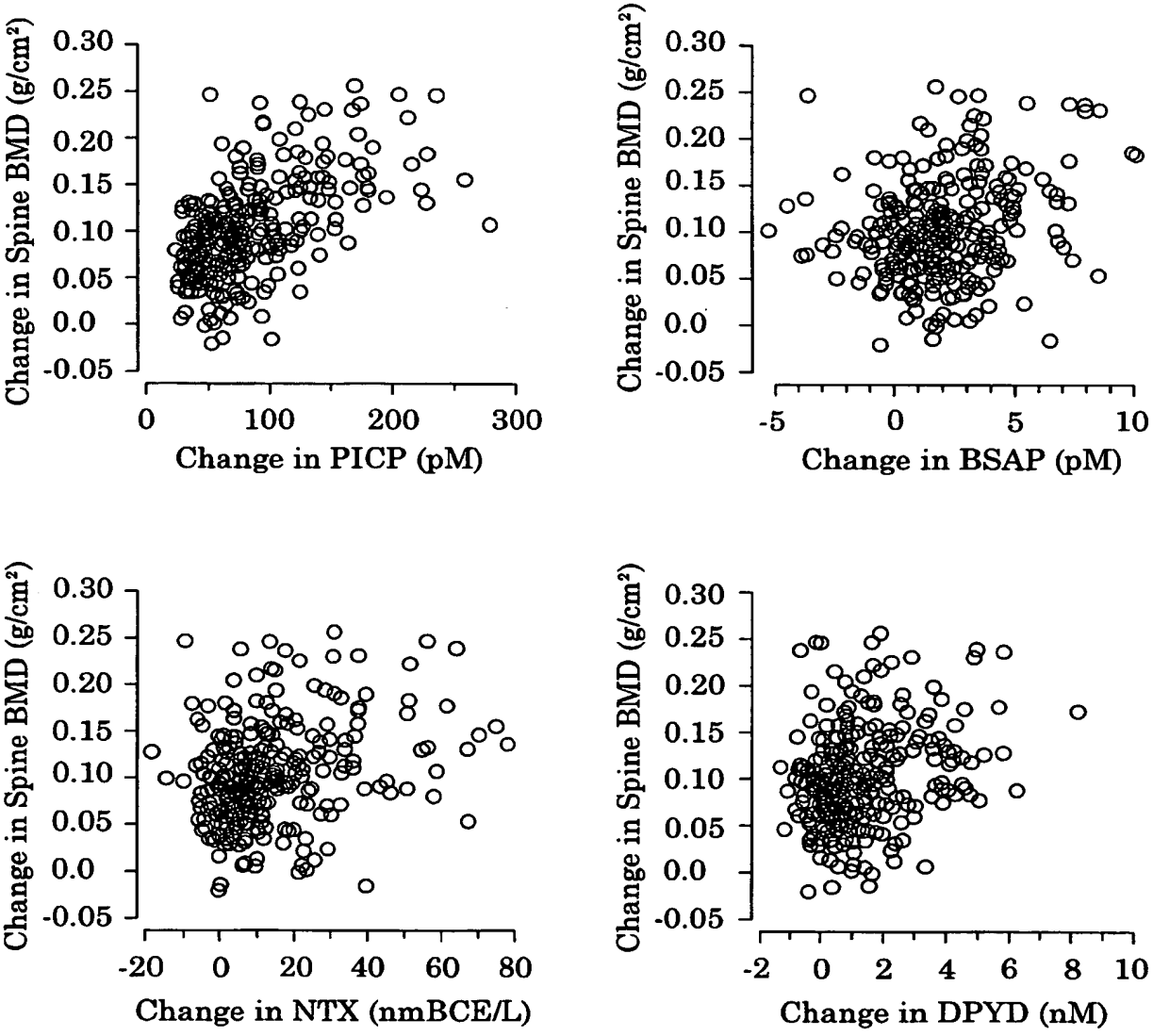

Change in Spine BMD (g/cm²)
0.30
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
0
100
200
300
Change in PICP (pM)
-5
0
5
10
Change in BSAP (pM)
-20
0
20
40
60
80
Change in NTX (nmBCE/L)
-2
0
2
4
6
8
10
Change in DPYD (nM)

FIG. 12

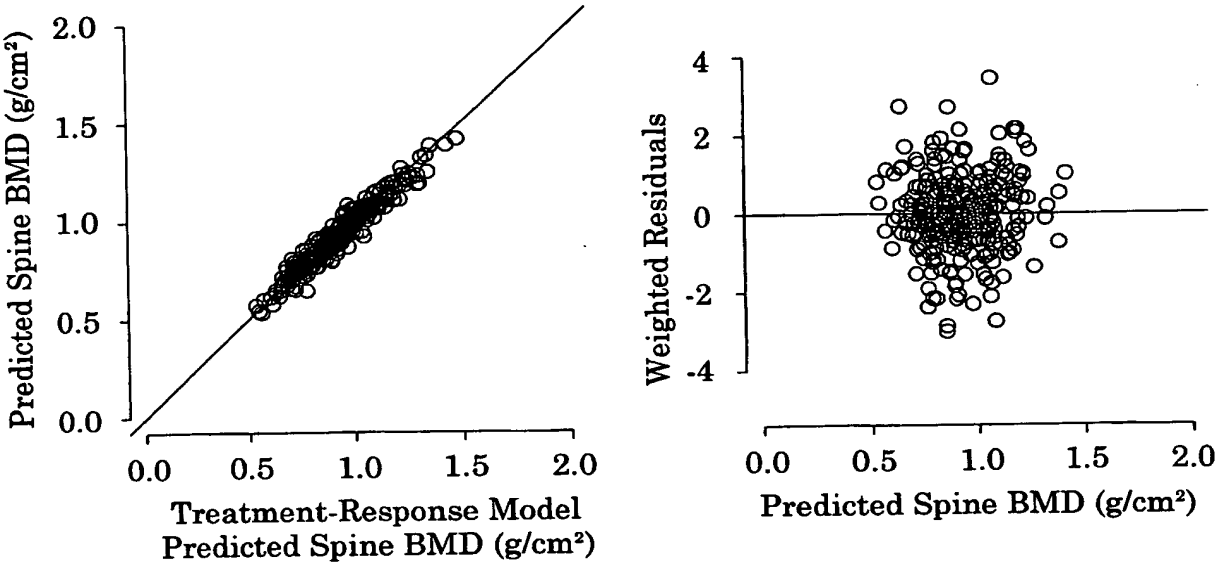

Predicted Spine BMD (g/cm²)
2.0
1.5
1.0
0.5
0.0
0.0
0.5
1.0
1.5
2.0
Treatment-Response Model
Predicted Spine BMD (g/cm²)
Weighted Residuals
4
2
0
-2
-4
0.0
0.5
1.0
1.5
2.0
Predicted Spine BMD (g/cm²)

FIG. 13

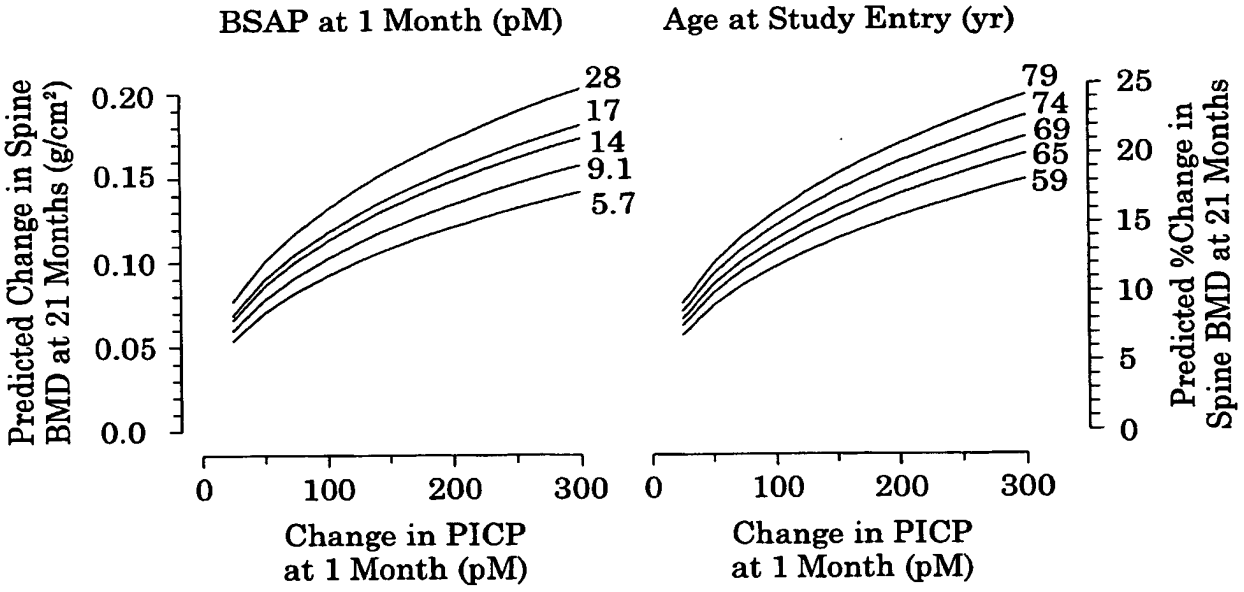

BSAP at 1 Month (pM)
Age at Study Entry (yr)
Predicted Change in Spine BMD at 21 Months (g/cm²)
0.20
0.15
0.10
0.05
0.0
28
17
14
9.1
5.7
79
74
69
65
59
25
20
15
10
5
0
Predicted %Change in Spine BMD at 21 Months
0
100
200
300
Change in PICP at 1 Month (pM)

FIG. 14

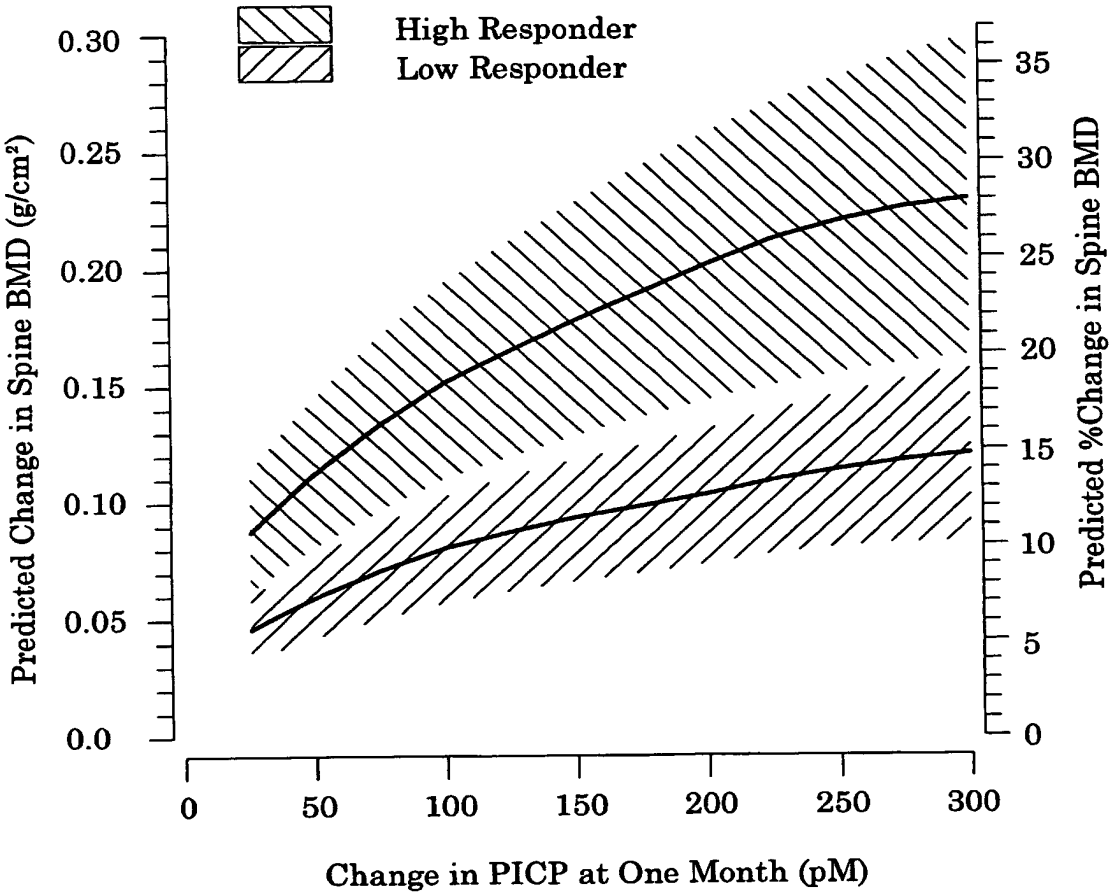

High Responder
Low Responder
Predicted Change in Spine BMD (g/cm²)
0.30
0.25
0.20
0.15
0.10
0.05
0.0
Predicted %Change in Spine BMD
35
30
25
20
15
10
5
0
0
50
100
150
200
250
300
Change in PICP at One Month (pM)

FIG. 15

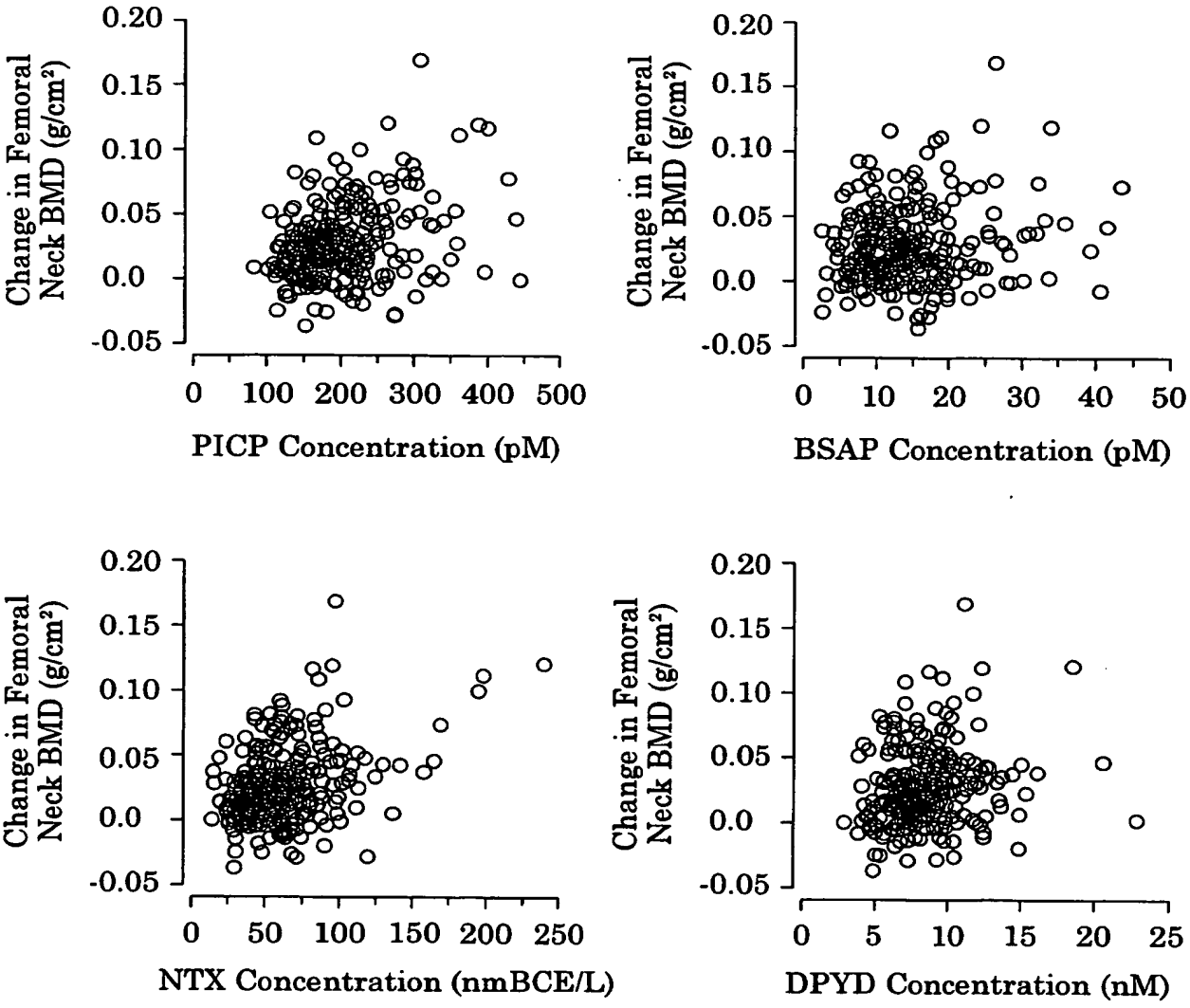
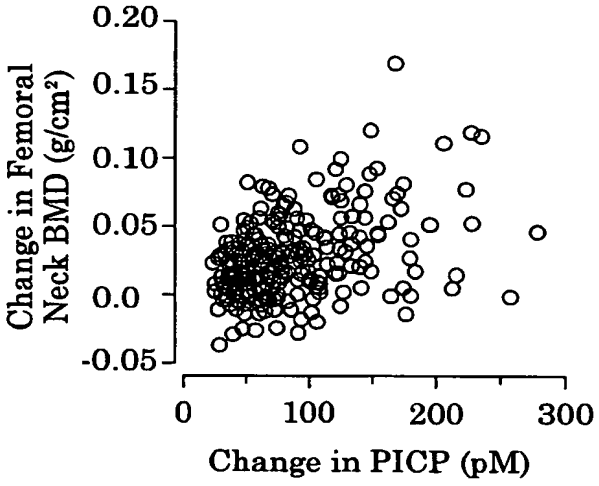
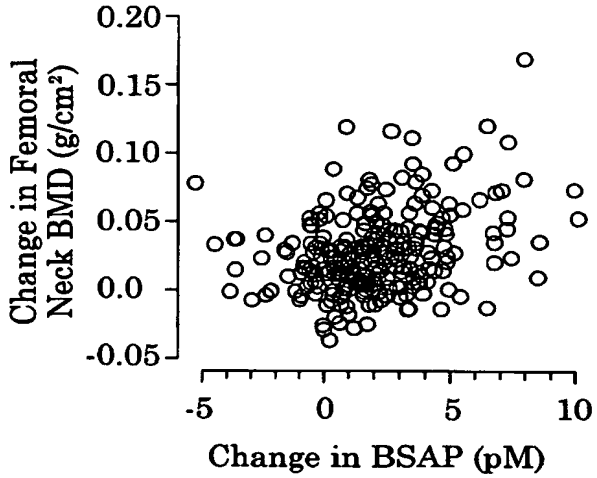
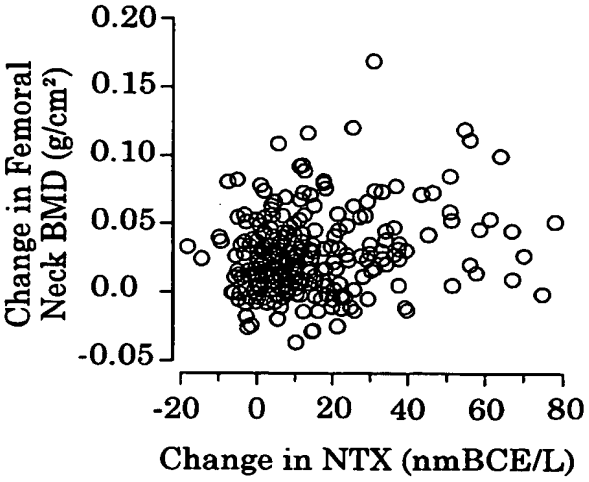

Change in Femoral Neck BMD (g/cm²)
0.20
0.15
0.10
0.05
0.0
-0.05
0 100 200 300 400 500
PICP Concentration (pM)
0 10 20 30 40 50
BSAP Concentration (pM)
0 50 100 150 200 250
NTX Concentration (nmBCE/L)
0 5 10 15 20 25
DPYD Concentration (nM)

FIG. 16


Change in Femoral Neck BMD (g/cm²)
0.20
0.15
0.10
0.05
0.0
-0.05
0
100
200
300
Change in PICP (pM)


Change in Femoral Neck BMD (g/cm²)
0.20
0.15
0.10
0.05
0.0
-0.05
-5
0
5
10
Change in BSAP (pM)


Change in Femoral Neck BMD (g/cm²)
0.20
0.15
0.10
0.05
0.0
-0.05
-20
0
20
40
60
80
Change in NTX (nmBCE/L)

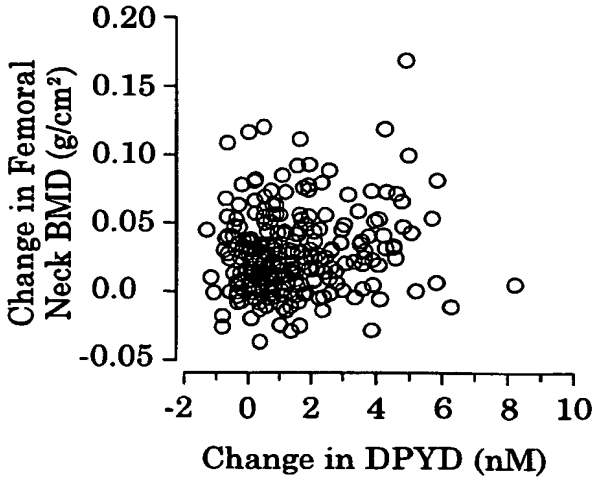

Change in Femoral Neck BMD (g/cm²)
0.20
0.15
0.10
0.05
0.0
-0.05
-2
0
2
4
6
8
10
Change in DPYD (nM)

FIG. 17

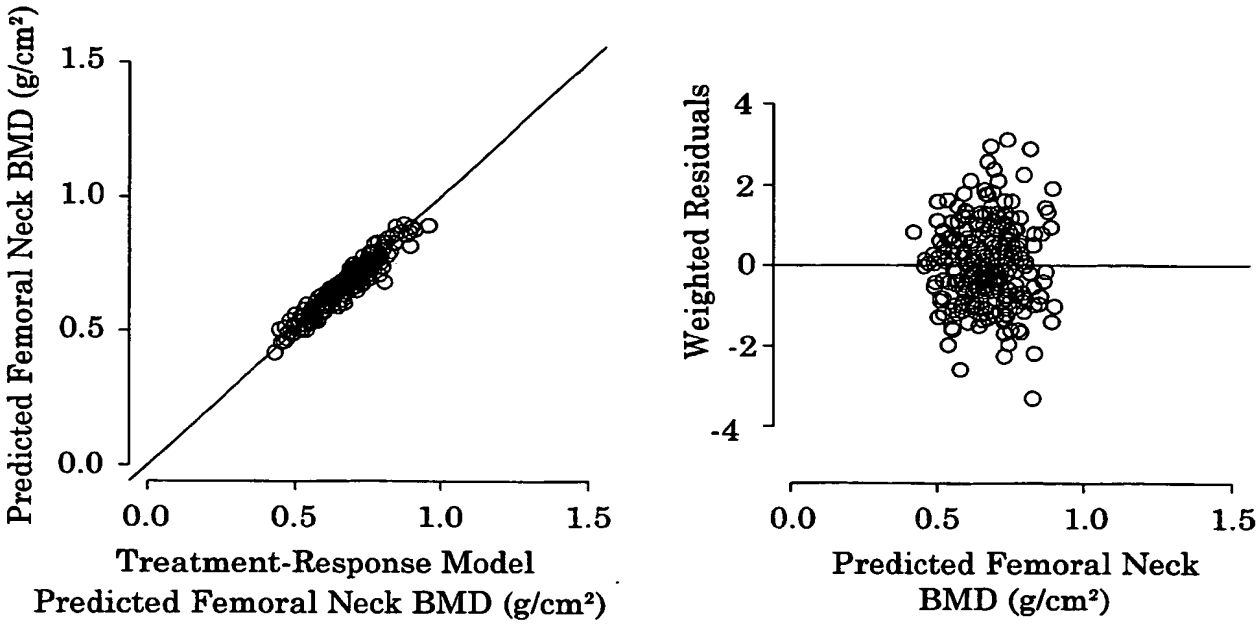

Predicted Femoral Neck BMD (g/cm²)
1.5
1.0
0.5
0.0
0.0
0.5
1.0
1.5
Treatment-Response Model
Predicted Femoral Neck BMD (g/cm²)
Weighted Residuals
4
2
0
-2
-4
0.0
0.5
1.0
1.5
Predicted Femoral Neck
BMD (g/cm²)

FIG. 18

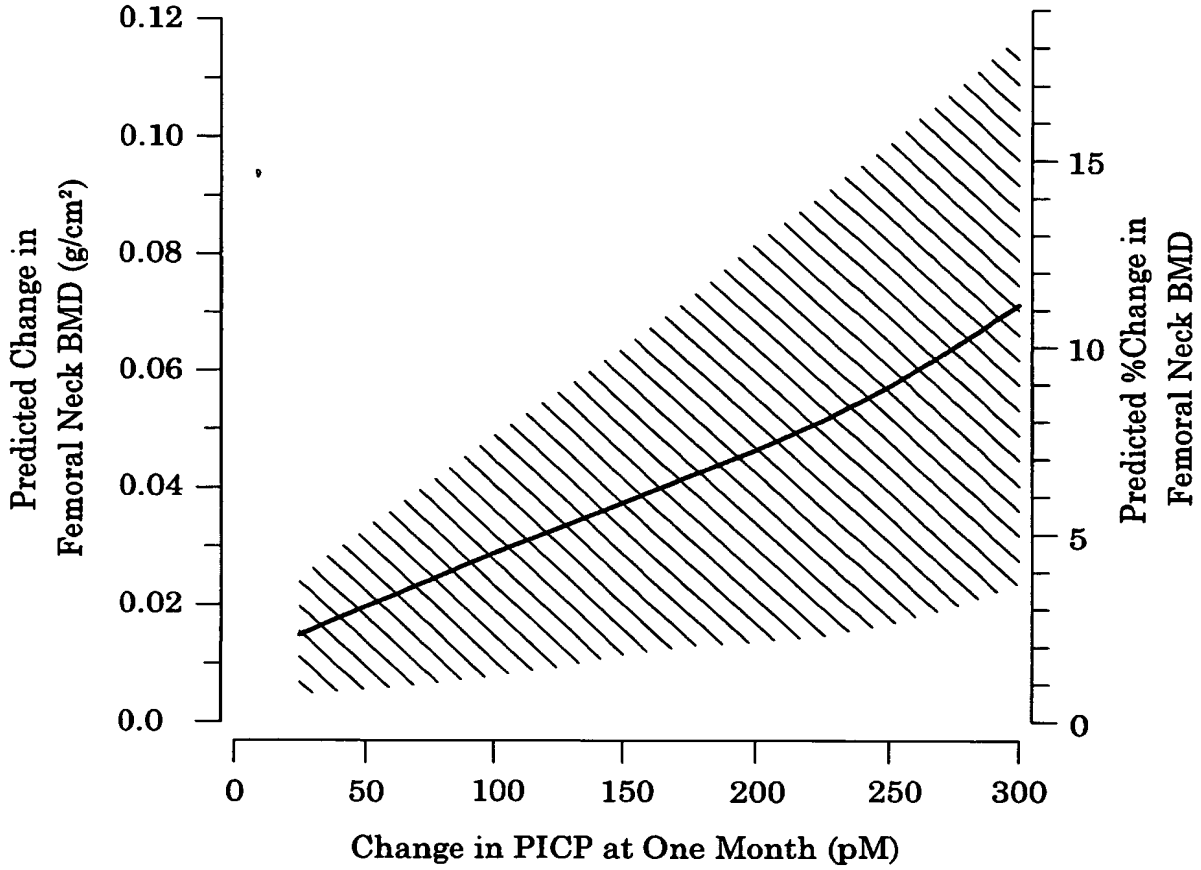
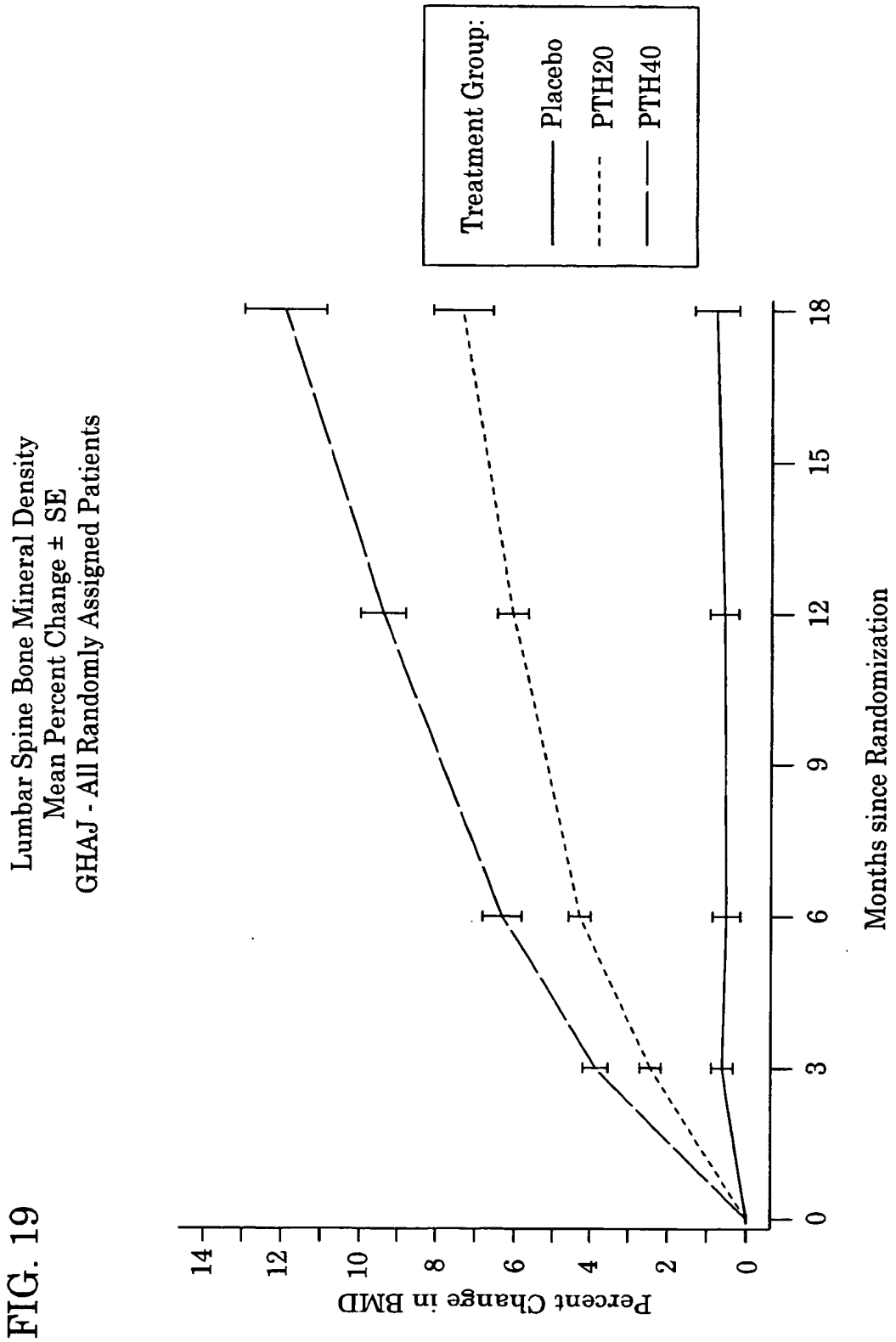

0.12
0.10
0.08
0.06
0.04
0.02
0.0
Predicted Change in Femoral Neck BMD (g/cm²)
15
10
5
0
Predicted %Change in Femoral Neck BMD
0
50
100
150
200
250
300
Change in PICP at One Month (pM)

FIG. 19


Lumbar Spine Bone Mineral Density
Mean Percent Change ± SE
GHAJ - All Randomly Assigned Patients
Treatment Group:
Placebo
PTH20
PTH40
Percent Change in BMD
0
2
4
6
8
10
12
14
Months since Randomization
0
3
6
9
12
15
18

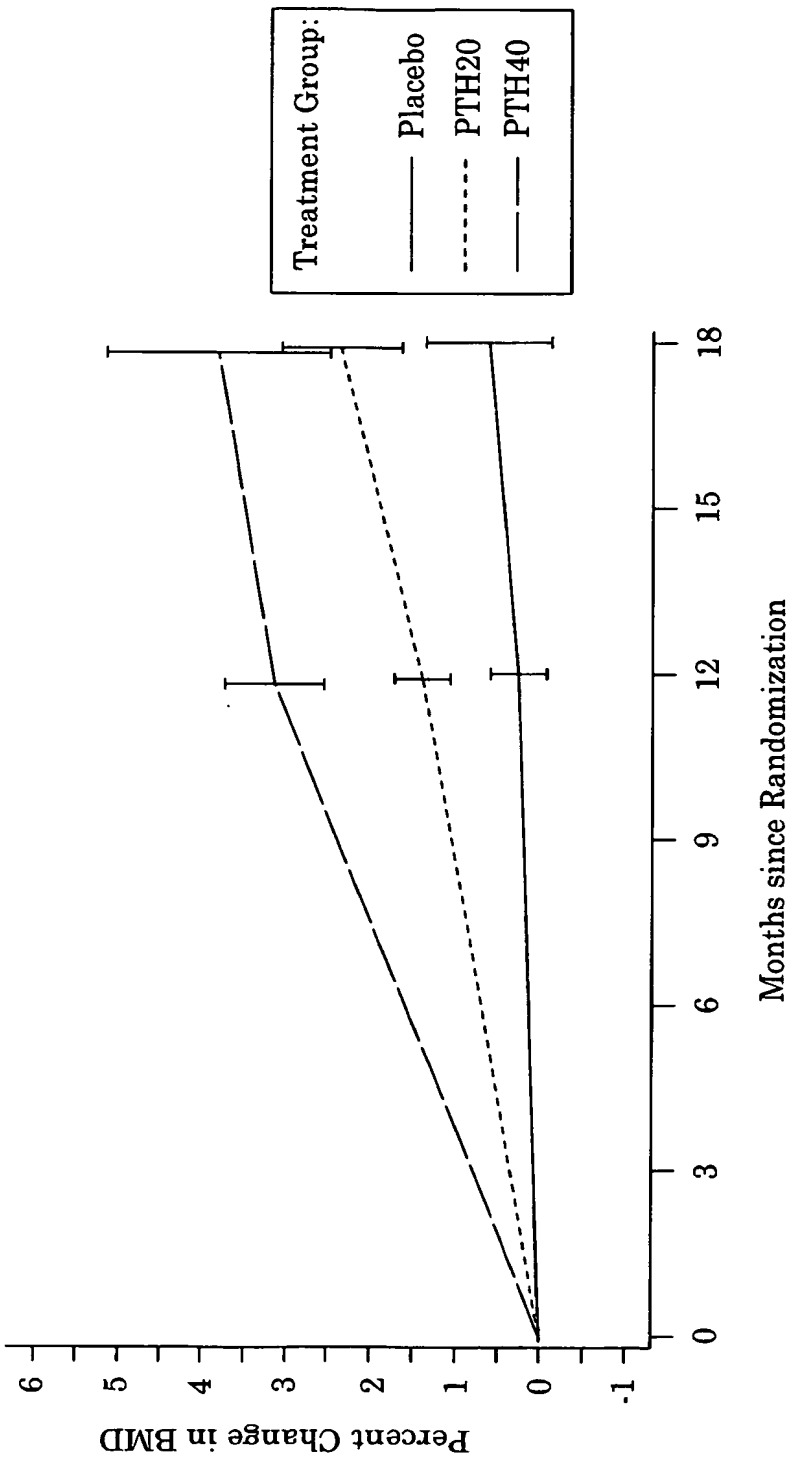

Femoral Neck Bone Mineral Density
Mean Percent Change ± SE
GHAJ - All Randomly Assigned Patients
Treatment Group:
Placebo
PTH20
PTH40
Percent Change in BMD
6
5
4
3
2
1
0
-1
0
3
6
9
12
15
18
Months since Randomization

FIG. 20

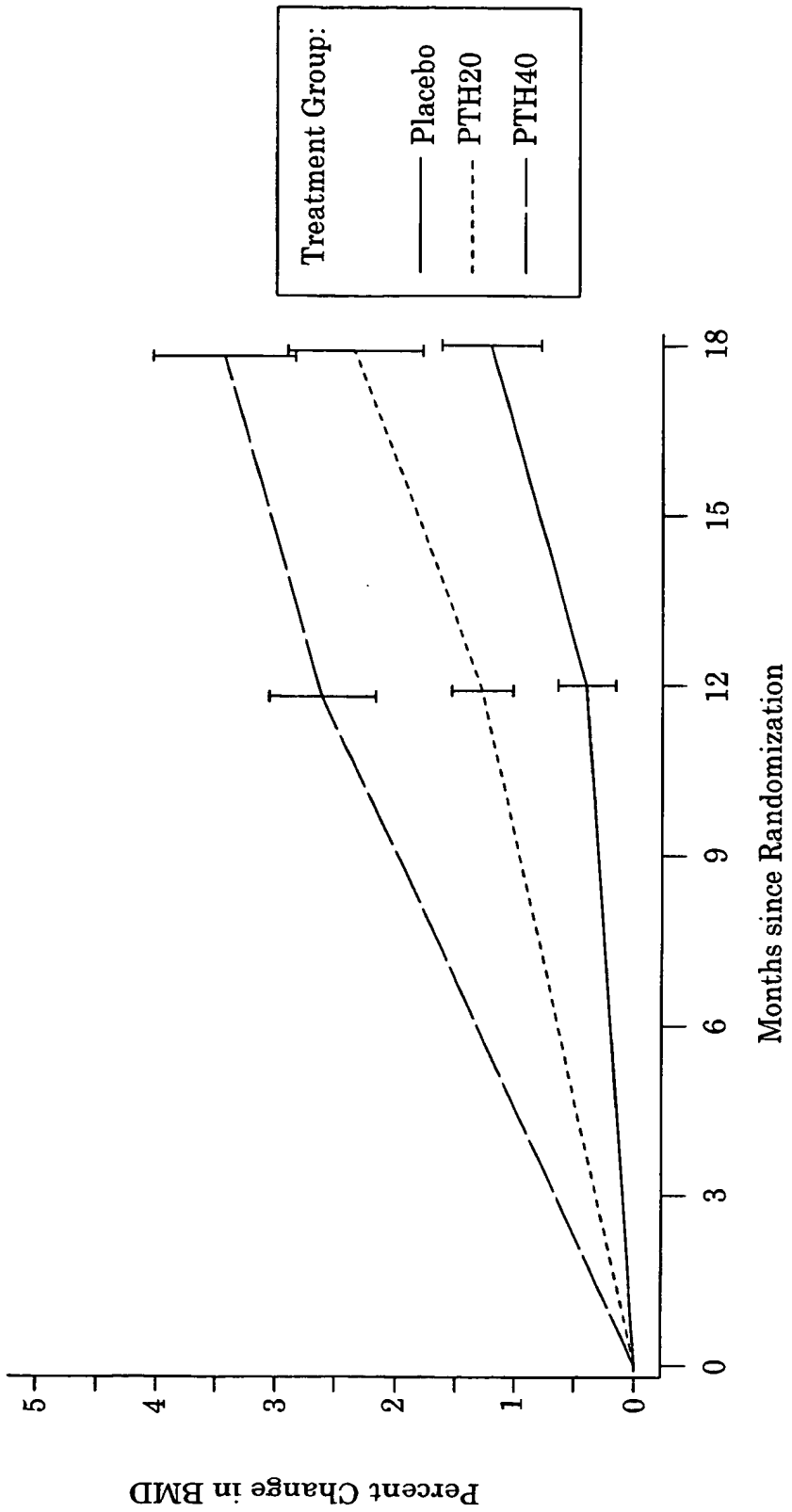

Total Hip Bone Mineral Density
Mean percent Change ± SE
GHAJ - All Randomly Assigned Patients
Treatment Group:
Placebo
PTH20
PTH40
Percent Change in BMD
0
1
2
3
4
5
0
3
6
9
12
15
18
Months since Randomization

FIG. 21

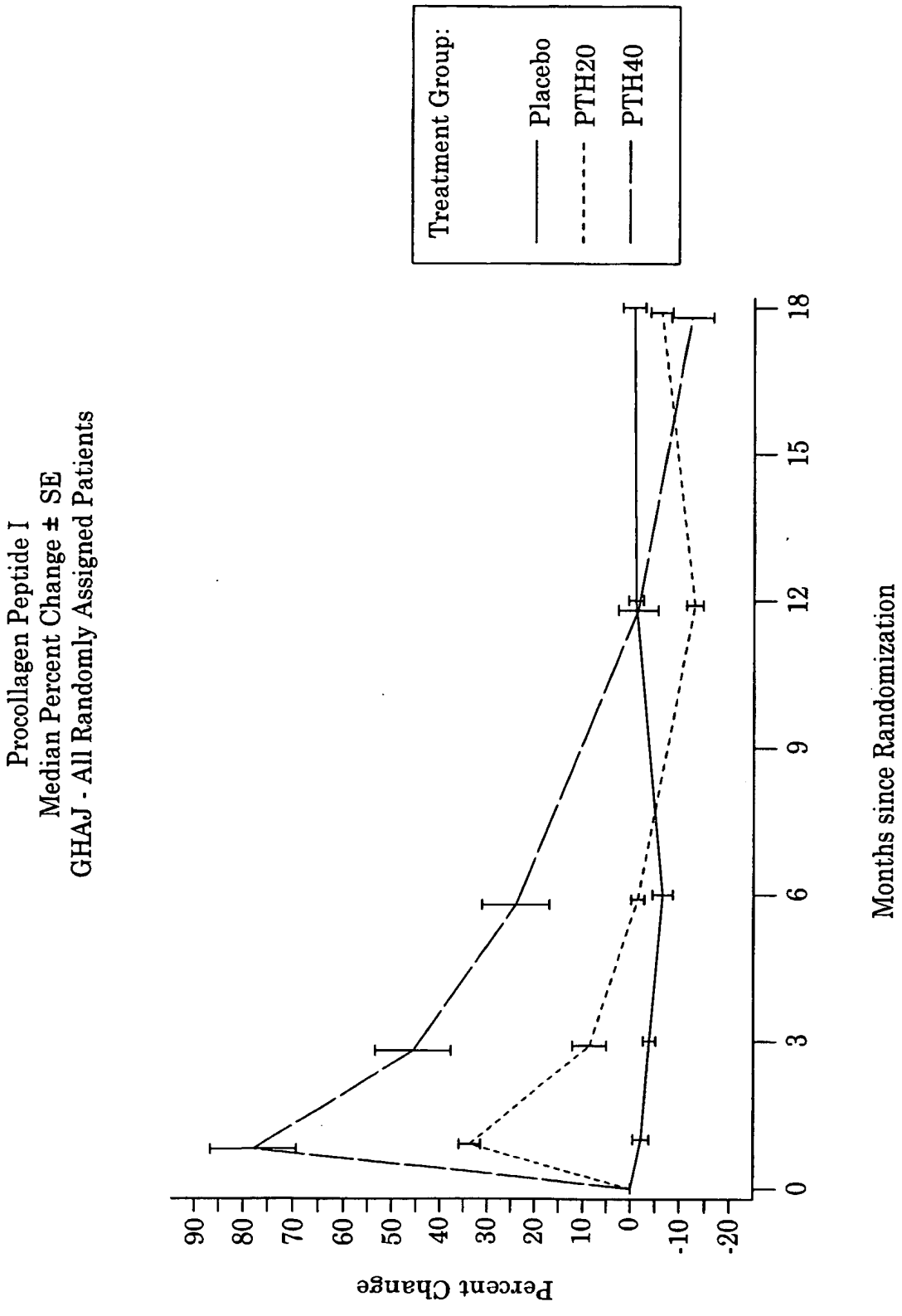

Procollagen Peptide I
Median Percent Change ± SE
GHAJ - All Randomly Assigned Patients
Treatment Group:
Placebo
PTH20
PTH40
Percent Change
90
80
70
60
50
40
30
20
10
0
-10
-20
0
3
6
9
12
15
18
Months since Randomization

FIG. 22

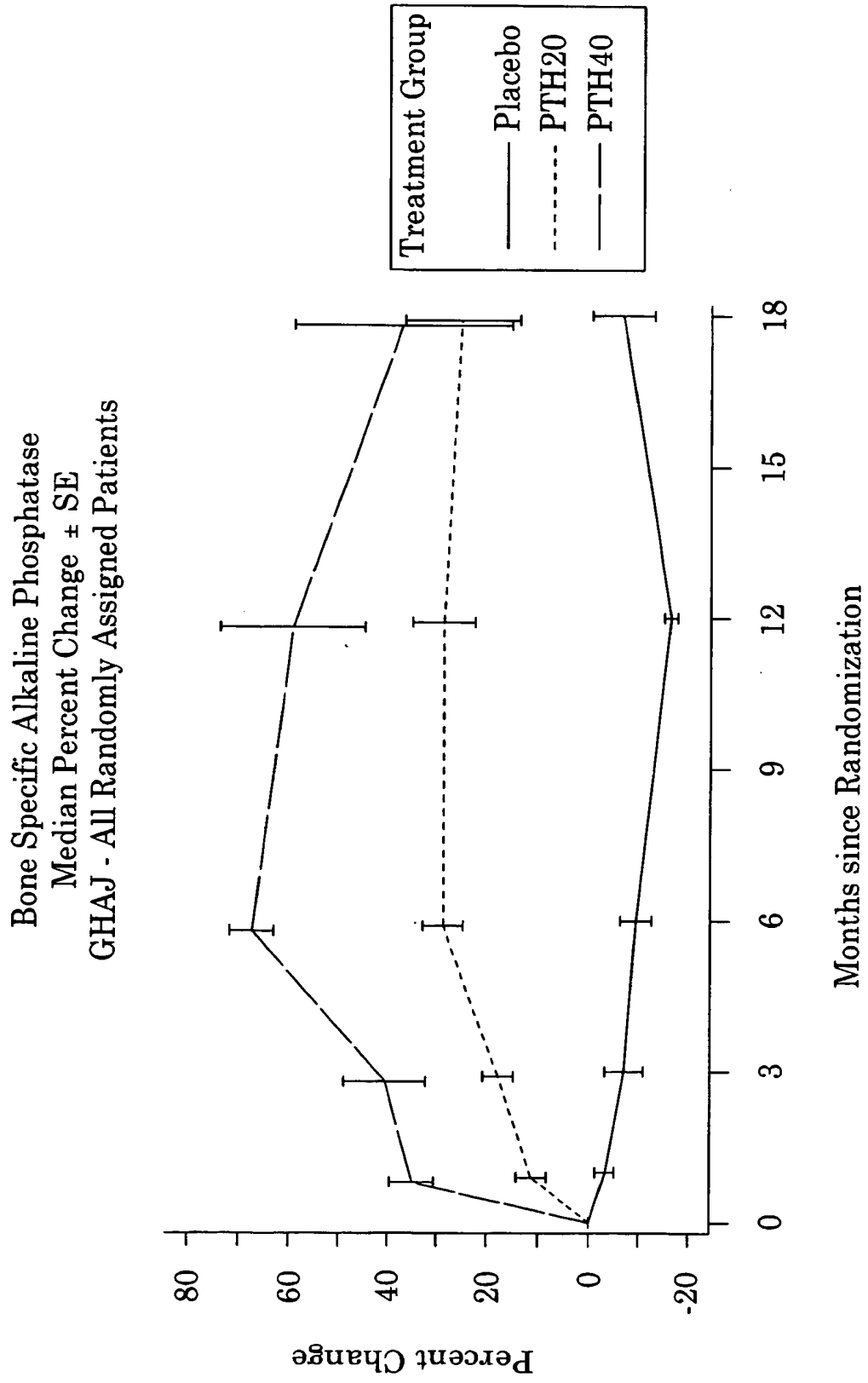

Bone Specific Alkaline Phosphatase
Median Percent Change ± SE
GHAJ - All Randomly Assigned Patients
Treatment Group
Placebo
PTH20
PTH40
Percent Change
80
60
40
20
0
-20
0
3
6
9
12
15
18
Months since Randomization

FIG. 23

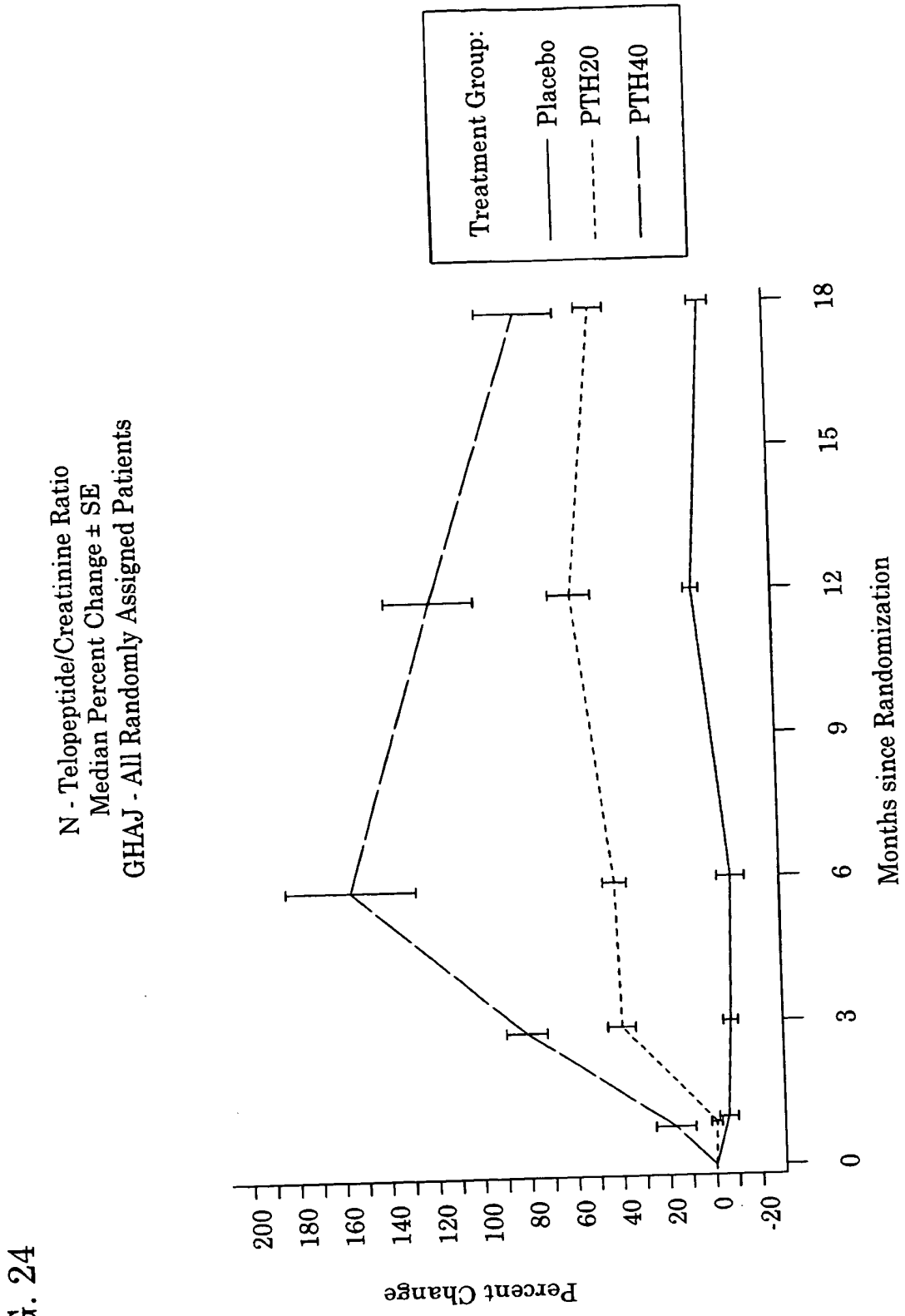

N - Telopeptide/Creatinine Ratio
Median Percent Change ± SE
GHAJ - All Randomly Assigned Patients
Treatment Group:
Placebo
PTH20
PTH40
Percent Change
200
180
160
140
120
100
80
60
40
20
0
-20
0
3
6
9
12
15
18
Months since Randomization

FIG. 24

FIG. 25

BMD Placebo-Response Model
Characterize changes in BMD over time

BMD Treatment-Response Model
Characterize effect of LY333334 on changes in BMD over time

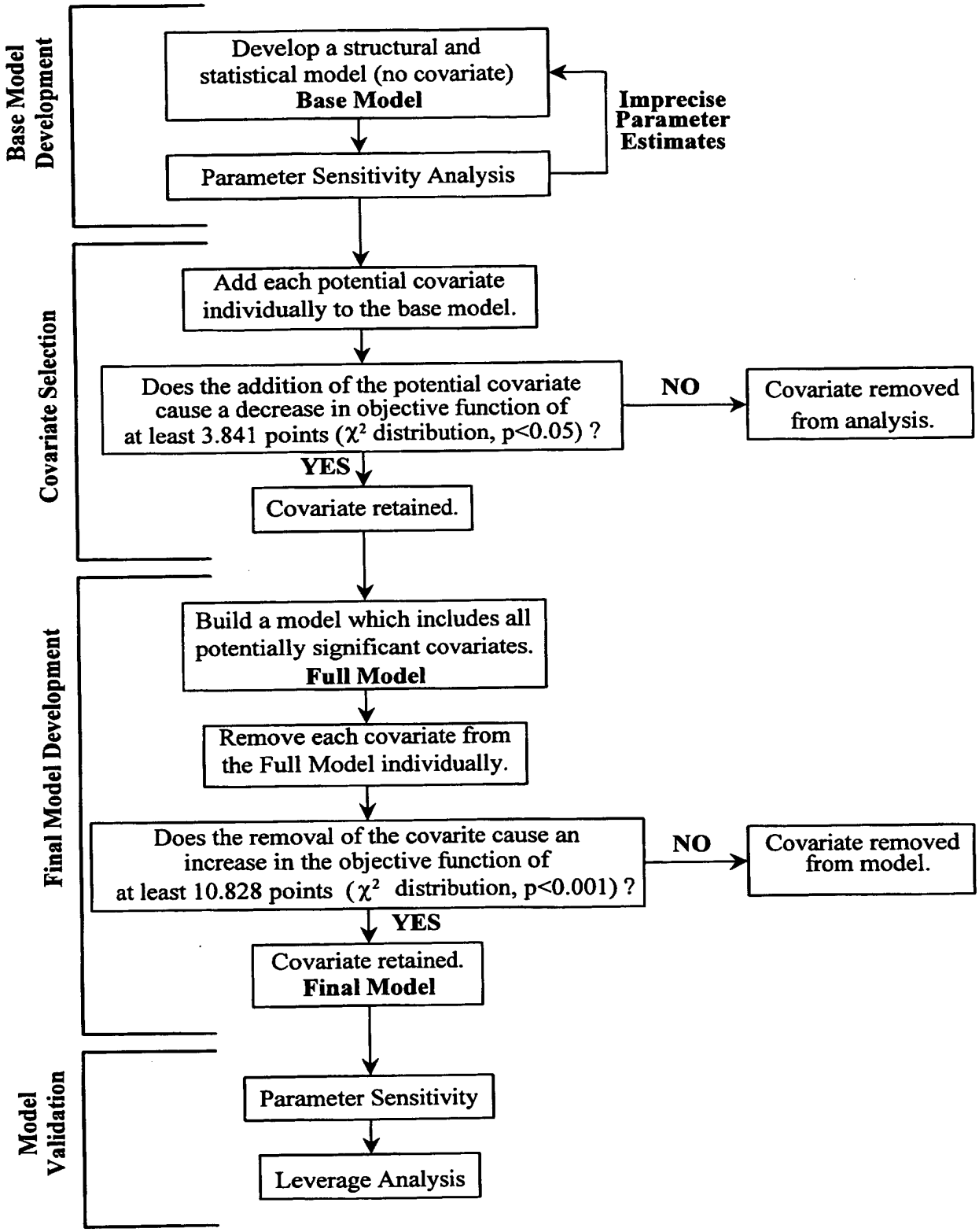
[Total Lumbar Spine BMD]

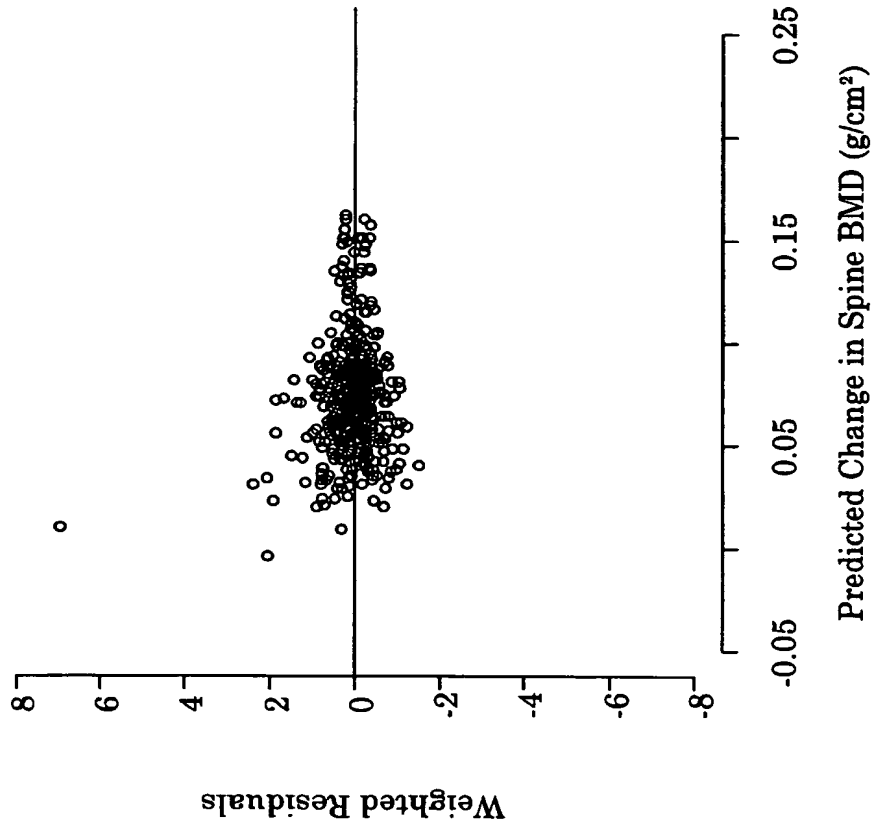
BCM Treatment-Response Model
Characterize effect of LY333334 on changes in BCM over time

[PICP, BSAP, NTX, and DPD]

Response-Indicator Neural Network
Characterize BCMs as early indicators of response to therepy
[Total Lumbar Spine BMD]
[PICP, BSAP, NTX, and DPD]

FIG. 26


Base Model Development
Develop a structural and statistical model (no covariate) Base Model
Parameter Sensitivity Analysis
Imprecise Parameter Estimates
Covariate Selection
Add each potential covariate individually to the base model.
Does the addition of the potential covariate cause a decrease in objective function of at least 3.841 points (χ^2 distribution, $p<0.05$) ?
NO
Covariate removed from analysis.
YES
Covariate retained.
Final Model Development
Build a model which includes all potentially significant covariates. Full Model
Remove each covariate from the Full Model individually.
Does the removal of the covarite cause an increase in the objective function of at least 10.828 points (χ^2 distribution, $p<0.001$) ?
NO
Covariate removed from model.
YES
Covariate retained. Final Model
Model Validation
Parameter Sensitivity
Leverage Analysis


Weighted Residuals
8
6
4
2
0
-2
-4
-6
-8
Predicted Change in Spine BMD (g/cm²)
-0.05
0.05
0.15
0.25

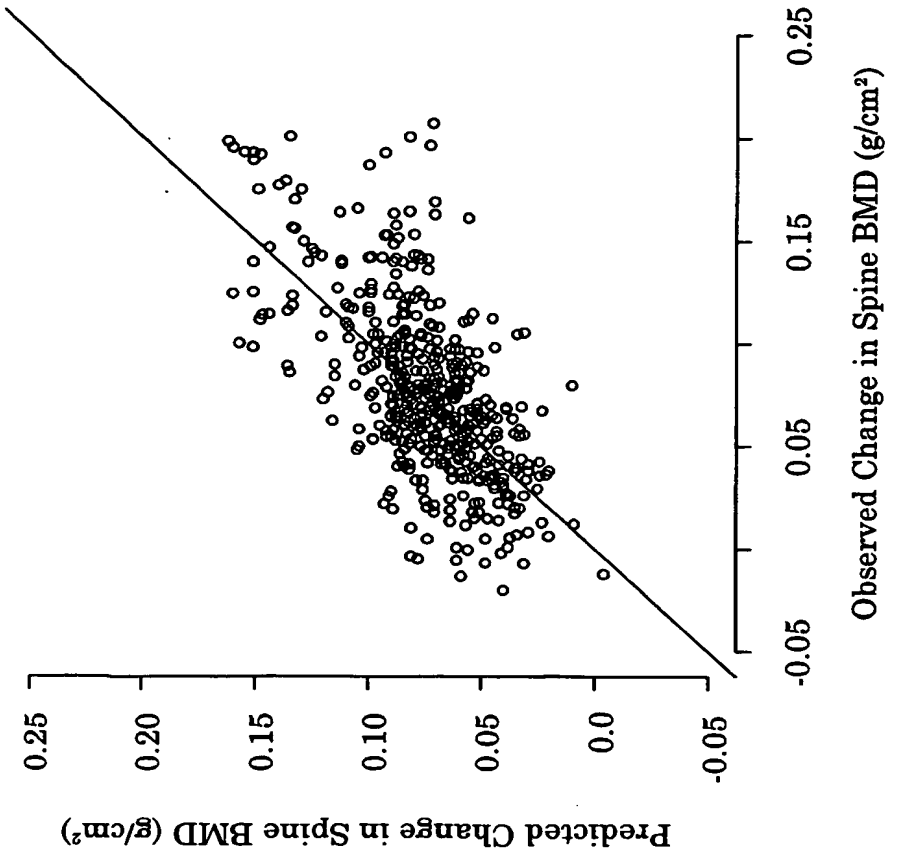

Predicted Change in Spine BMD (g/cm²)
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
Observed Change in Spine BMD (g/cm²)
-0.05
0.05
0.15
0.25

FIG. 27

Predicted Change in Spine BMD at 12 Months (g/cm²)
0.16
0.12
0.08
0.04
0.0
20-µg Treatment Group
Females
Males
0
100
200
300
Change in PICP at 1 Month (pM)
40-µg Treatment Group
Females
Males
0
100
200
300
Change in PICP at 1 Month (pM)
Predicted %Change in Spine BMD at 12 Months
20
15
10
5
0

FIG. 28

Predicted Change in Spine BMD at 12 Months (g/cm²)
0.16
0.12
0.08
0.04
0.0
Females
Age at Study Entry (years)
78
64
42
0
100
200
300
Change in PICP at 1 Month (pM)
Predicted %Change in Spine BMD at 12 Months
20
15
10
5
0
Males
Age at Study Entry (years)
78
42
0
100
200
300
Change in PICP at 1 Month (pM)

FIG. 29

FIG. 30

Predicted Change in Spine BMD at 12 Months (g/cm²)
0.16
0.12
0.08
0.04
0.0
PICP at Baseline (pM)
Females
188
122
74
0
100
200
300
Change in PICP at 1 Month (pM)
PICP at Baseline (pM)
Males
188
122
74
0
100
200
300
Change in PICP at 1 Month (pM)
Predicted %Change in Spine BMD at 12 Months
20
15
10
5
0

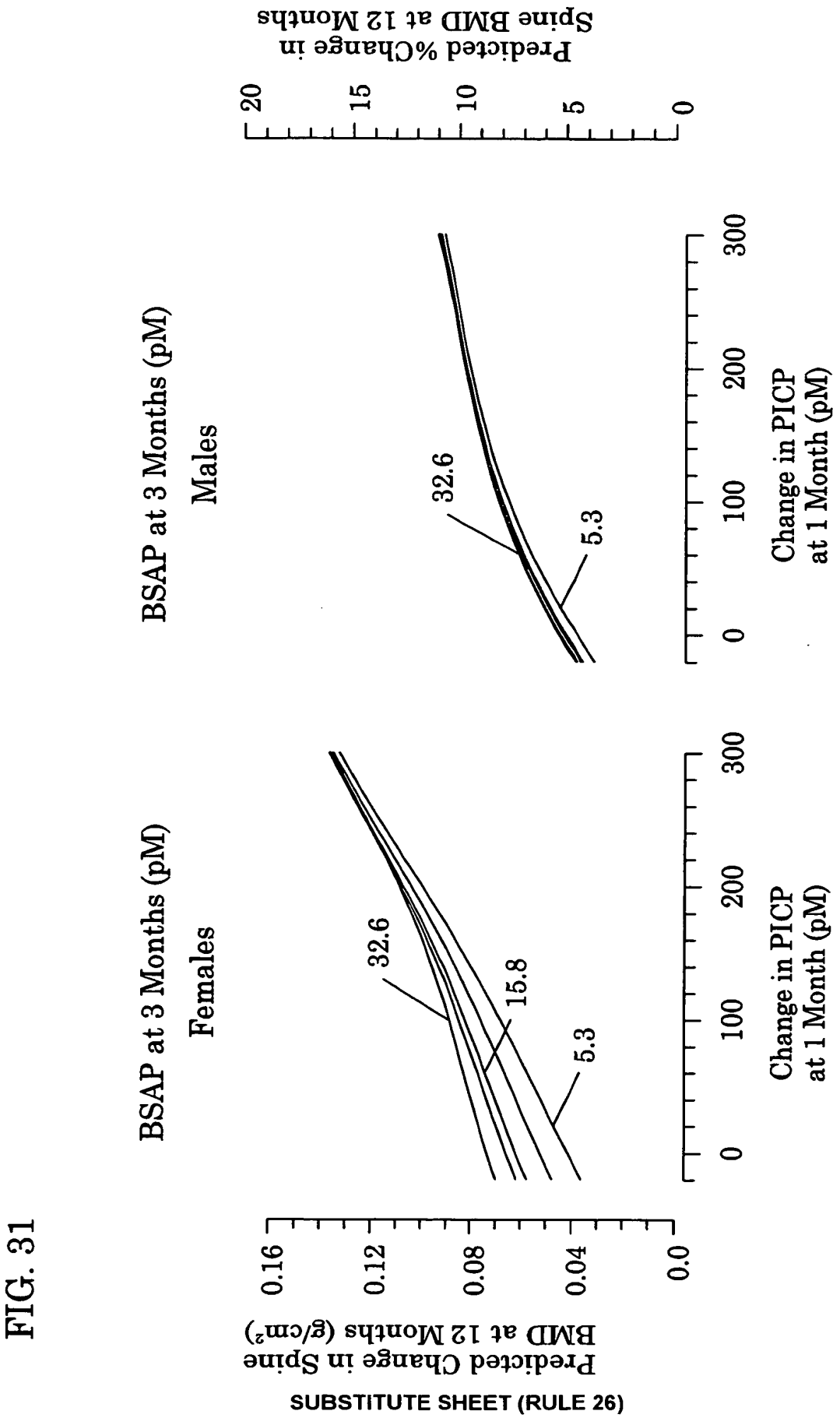
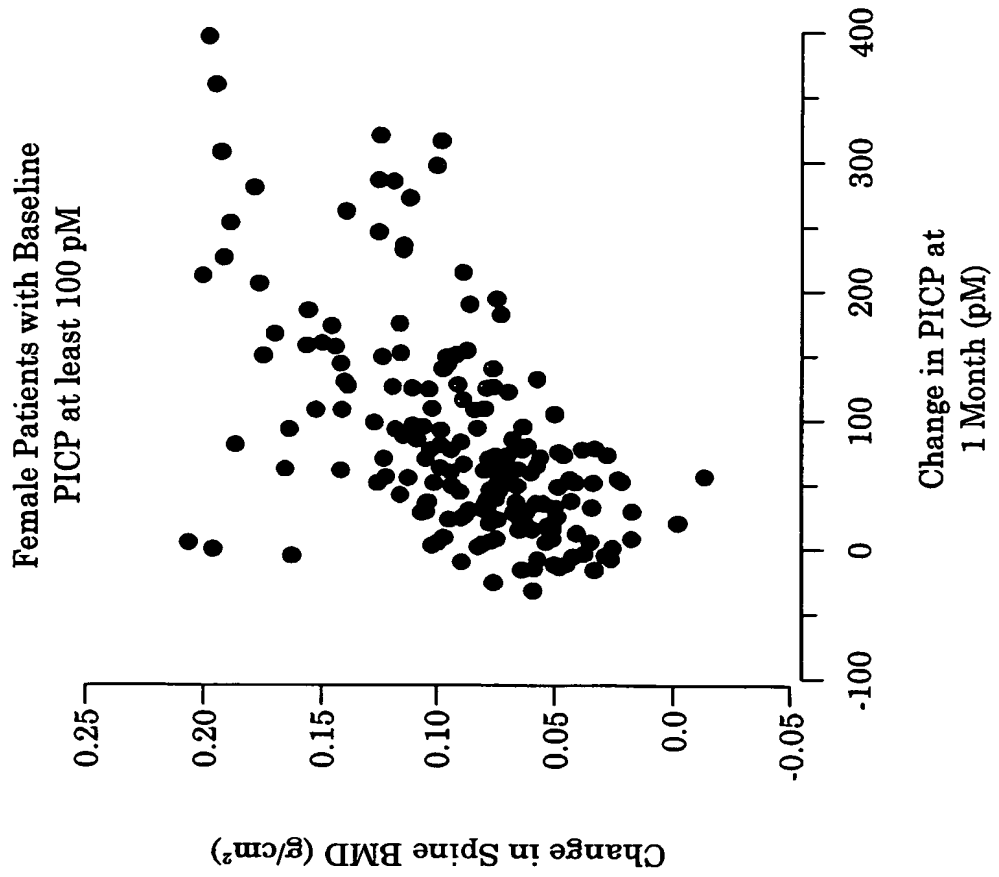

Predicted Change in Spine BMD at 12 Months (g/cm²)
0.16
0.12
0.08
0.04
0.0
BSAP at 3 Months (pM)
Females
32.6
15.8
5.3
0
100
200
300
Change in PICP at 1 Month (pM)
BSAP at 3 Months (pM)
Males
32.6
5.3
0
100
200
300
Change in PICP at 1 Month (pM)
Predicted %Change in Spine BMD at 12 Months
20
15
10
5
0

FIG. 31


Female Patients with Baseline
PICP at least 100 pM
Change in PICP at
1 Month (pM)
Change in Spine BMD (g/cm²)
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
-100
0
100
200
300
400

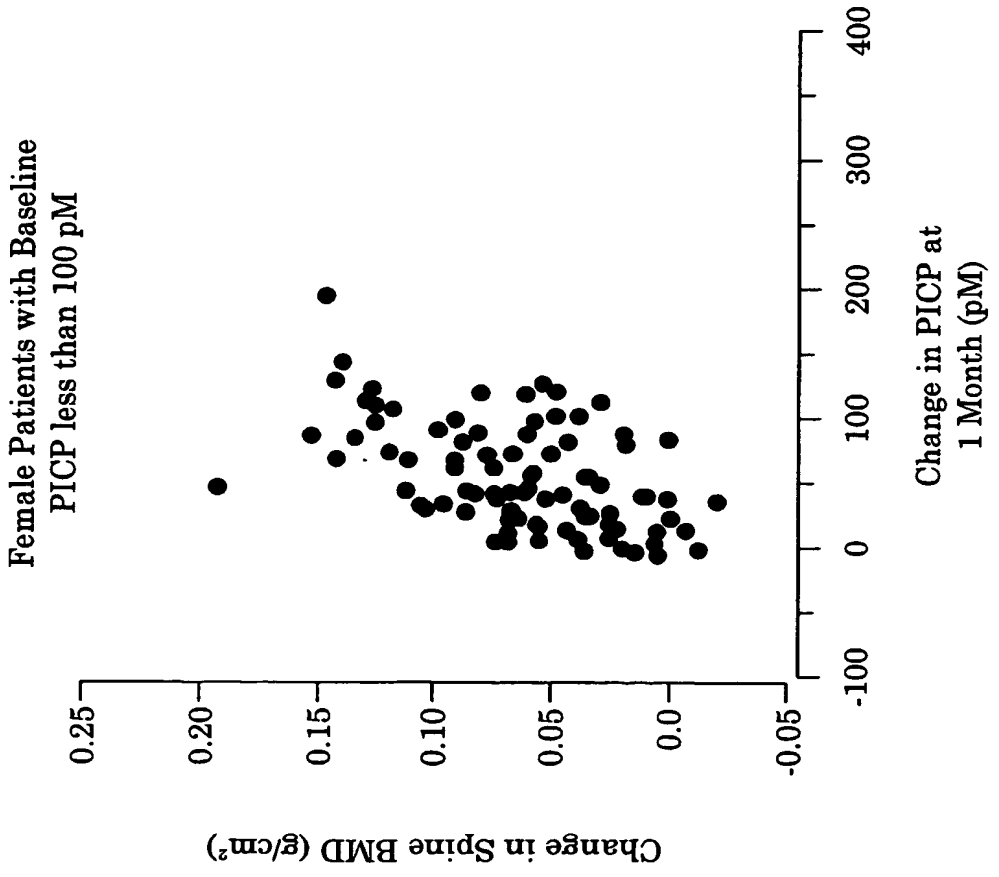

Female Patients with Baseline
PICP less than 100 pM
Change in PICP at
1 Month (pM)
Change in Spine BMD (g/cm²)
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
-100
0
100
200
300
400

FIG. 32

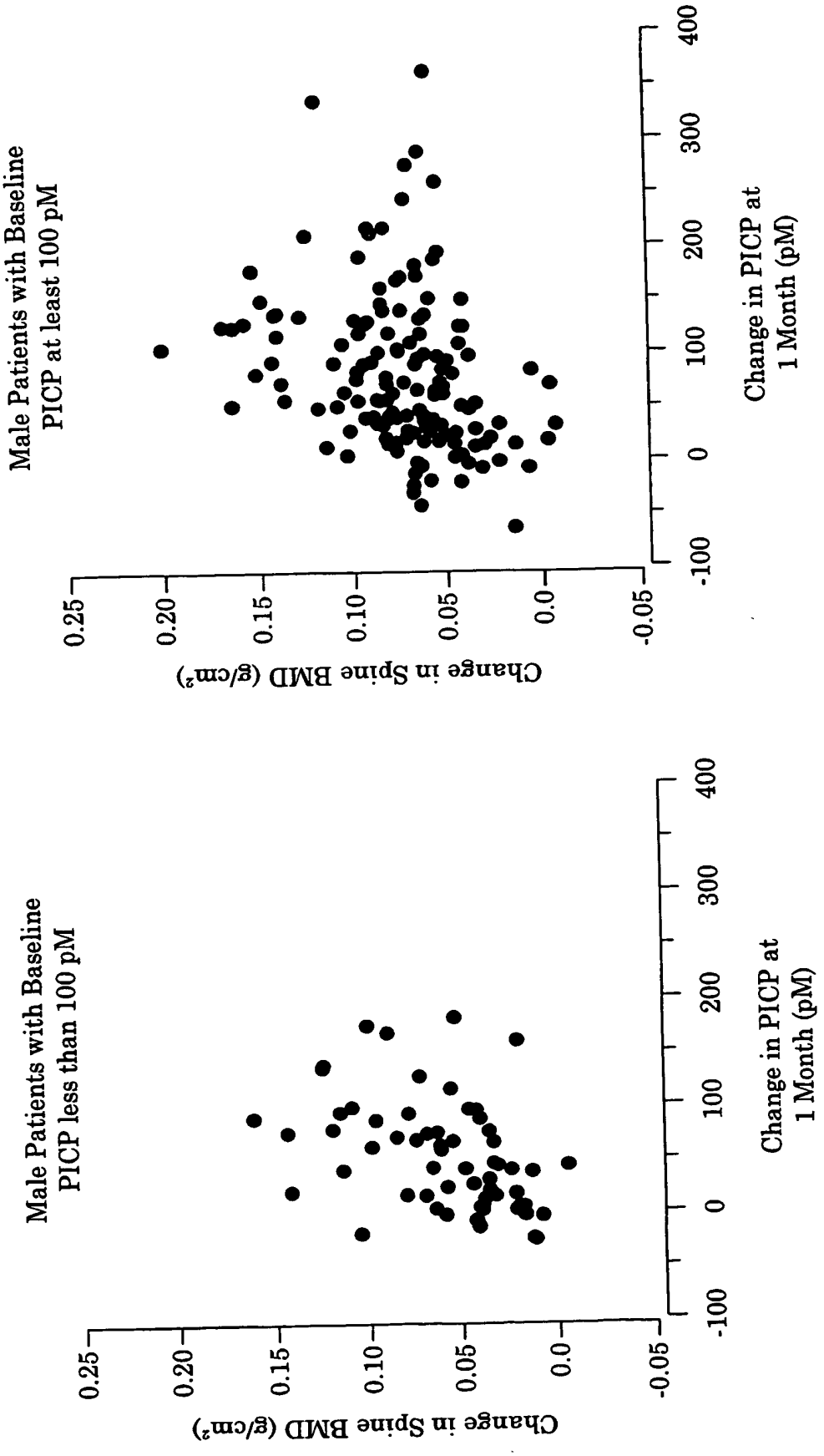
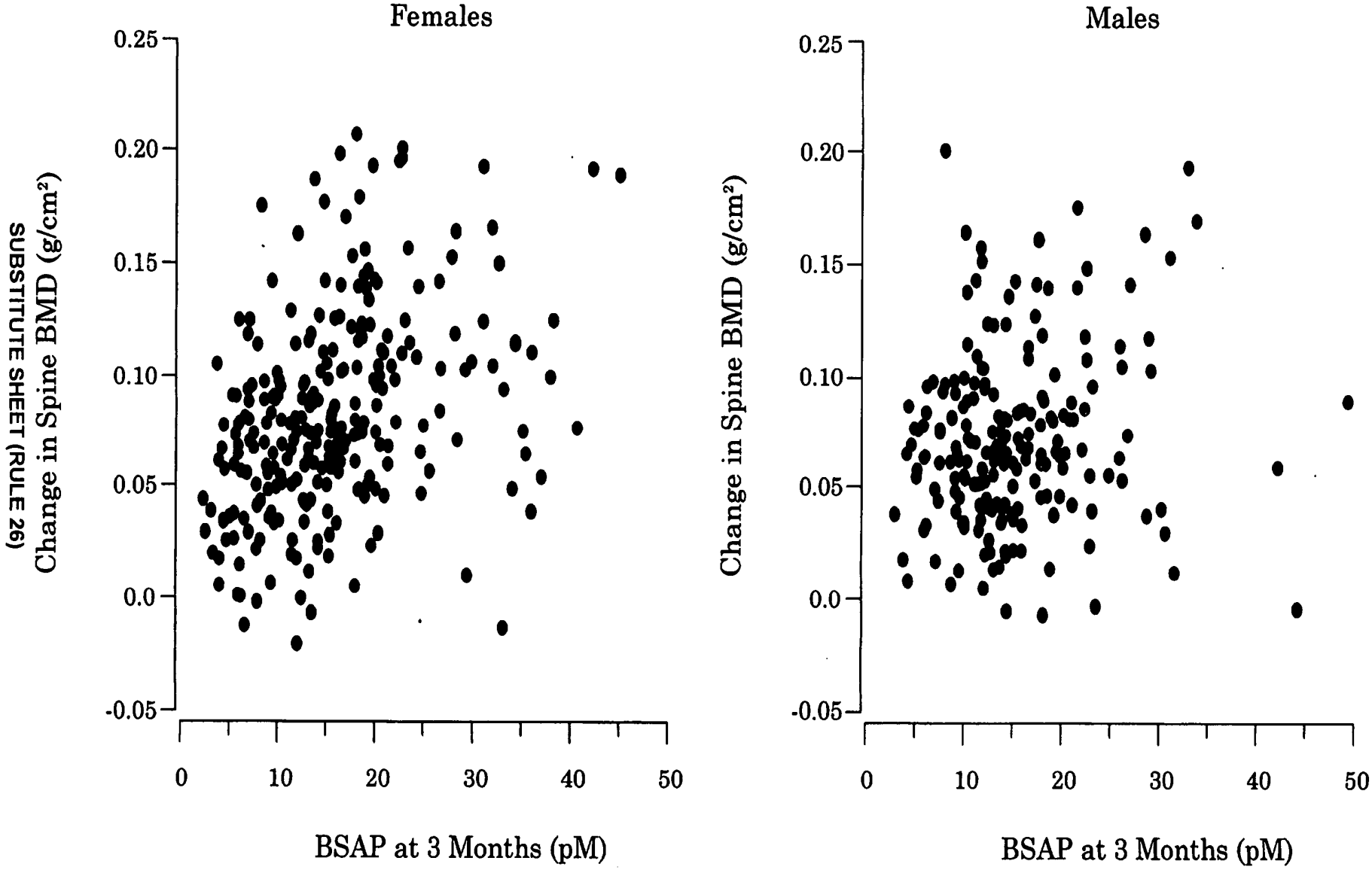

Male Patients with Baseline
PICP at least 100 pM
Change in Spine BMD (g/cm²)
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
-100
0
100
200
300
400
Change in PICP at
1 Month (pM)
Male Patients with Baseline
PICP less than 100 pM
Change in Spine BMD (g/cm²)
0.25
0.20
0.15
0.10
0.05
0.0
-0.05
-100
0
100
200
300
400
Change in PICP at
1 Month (pM)

FIG. 33

FIG. 34



SUBSTITUTE SHEET (RULE 26)